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GI&Hepatology News

December 2021

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Michigan Medicine

Short of longitudinal studies, this is the closest we'll get to a linkage, says Dr. Elliot Tapper.

Drink up: Large study shows coffee benefits liver

BY THOMAS R. COLLINS
MDedge News

Drinking more than three cups of caffeinated coffee a day is associated with less liver stiffness, according to an analysis of a nationally representative survey, which was recently published in Clinical Gastroenterology and Hepatology (2021 Sep. doi: 10.1016/j.cgh.2021.09.042).

The study is likely the most rigorous look to date on the benefits of coffee on liver health in the U.S. It was based on data from the National Health and Nutrition Examination Survey (NHANES), in which participants were asked about what they eat and drink. Crucially, in 2017, NHANES began to include elastography (FibroScan) of participants' liver stiffness, not because of suspected problems with the liver but as across-the-board evaluations of all participants.

"Because it's an unselected population for FibroScan and because of the

See **Coffee** · *page 17*

AGA Clinical Practice Update: Expert Review

Managing pain in gut-brain interaction disorders

BY JIM KLING
MDedge News

An American Gastroenterological Association clinical practice update expert review for gastrointestinal pain in disorders of gut-brain interaction (DGBI), published in Clinical Gastroenterology and Hepatology (2021 Jul 3. doi: 10.1016/j.cgh.2021.07.006), emphasizes patient-physician collaboration and improvement of patient understanding of the pathways and mechanisms of pain sensations. It is aimed at management of patients in whom pain persists after first-line therapies fail to resolve visceral causes of pain.

DGBIs include irritable bowel syndrome, functional dyspepsia, and centrally mediated abdominal pain syndrome, according to Laurie Keefer, PhD, AGAF, of the division of gastroenterology at Icahn School of Medicine at Mount Sinai, New York, and colleagues. Initial treatment usually focuses on visceral triggers of pain such as food and bowel movements, but this approach is ineffective for many.

Cognitive, affective, and

See **Pain** · *page 47*

INSIDE

'Deep learning' AI shows benefit in colonoscopy in U.S. population

BY HEIDI SPLETE
MDedge News

Adenoma miss rates were significantly lower with the use of an artificial intelligence (AI)–based computer-aided detection (CADe) system than with high-definition white light (HDWL), according to a new prospective, multicenter, single-blind randomized study based on data from more than 200 colonoscopies.

Missed adenomas can be generally categorized as adenomas fully obscured from the visual field or

See **Colonoscopy** · *page 35*

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LETTER FROM THE EDITOR

Supporting clinician well-being and organizational resilience

The COVID-19 pandemic highlighted a major gap in our institutional infrastructure in medicine – specifically, the absence of established policies and programs to support clinician well-being and organizational resilience. In a 2020 report, the National Academy of Medicine advocated for "fixing the workplace," rather than "fixing the worker," as a more sustainable mechanism to advance physician well-being and foster organizational resilience. According to the report, "A resilient organization, or one that has matched job demands with job resources for its workers and that has created a culture of connection, transparency, and improvement, is better positioned to achieve organizational objectives during ordinary times and also to weather challenges during times of crisis" (Sinsky CA et al. "Organizational Evidence-Based and Promising Practices for Improving Clinician Well-Being." National Academy of Medicine. Nov. 2, 2020. https://nam.edu/organizational-evidence-based-and-promising-practices-for-improving-clinician-well-being/).


Dr. Adams

The report highlights six domains of evidence-based practices to support organizational resilience and improve clinician well-being: organizational commitment, workforce assessment (such as measurement of physician wellbeing and burnout); leadership (including shared accountability, distributed leadership, and the emerging role of a chief wellness officer), policy (such as eliminating and/or re-envisioning policies and practices that interfere with clinicians' ability to provide high-quality patient care), efficiency (such as minimizing administrative tasks to allow clinicians to focus on patient care), and support (such as providing resources and/or policies to support work-life balance, fostering a culture of connection at work). While many organizations (including both academic and community practices) already have begun to invest in this transformation, I urge you to think creatively about whether there is more your practice can do at an organizational level to support and sustain clinician well-being and prevent burnout.

In this month's issue of GIHN, we highlight AGA's new Clinical Practice Guideline on Coagulation in Cirrhosis, as well as results from a study confirming the benefits of coffee for liver health (welcome news to the caffeine-lovers among us!). We also report on a novel text-based patient-education intervention that aims to connect patients newly diagnosed with colorectal cancer to valuable resources and support.

Thank you for your dedicated readership – we look forward to continuing to bring you engaging, clinically relevant content in 2022!

Megan A. Adams, MD, JD, MSc
Editor in Chief

aga community

Top case

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. Here's a preview of a recent popular clinical discussion:

Robert Herman, MD, wrote in "Rectal lesion":

A 42-year-old healthy female was seen by me for symptoms of non-ulcer dyspepsia that was unresponsive to H2 blockers and for assessment for screening colonoscopy. Her father had developed colon cancer at the age of 50. She denied changes in bowel habits, pattern, rectal bleeding, or melena. An EGD revealed a medium-sized hiatal hernia and LA Grade B esophagitis that responded well to an OTC PPI qd.

A colonoscopy was performed and revealed a 4-cm anterior rectal "bulge" just above the hemorrhoidal plexus, appearing somewhat firm and mobile on probing the lesion with a closed biopsy forceps, and a 1 cm sessile IC valve adenomatous polyp.

And then the endoscopic medical assistant made a comment that changed everything. Read the full case discussion: https://community.gastro.org/posts/25568.

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Blood-based panel catches early-stage HCC

BY BRANDON MAY
MDedge News

A blood-based biomarker panel that includes DNA and protein markers featured a 71% sensitivity at 90% specificity for the detection of early-stage hepatocellular carcinoma (HCC) compared with the GALAD (gender, age, a-fetoprotein [AFP], Lens culinaris agglutinin-reactive AFP [AFP-L3], and des-gamma-carboxy-prothrombin [DCP]) score or AFP alone, according to research findings. The panel reportedly performed well in subgroups based on sex, presence of cirrhosis, and liver disease etiology.

The study, which included inpatients with HCC and controls without HCC but underlying liver disease, suggests the panel could be utilized in the detection of early-stage disease in patients with well-established risk factors for HCC. Ultimately, this may lead to earlier treatment initiation and potentially improved clinical outcomes.

"A blood-based marker panel that detects early-stage HCC with higher sensitivity than current biomarker-based approaches could substantially benefit patients undergoing HCC surveillance," wrote study authors Naga Chalasani, MD, AGAF, of Indiana University, Indianapolis, and colleagues. Their report is in Clinical Gastroenterology and Hepatology (2020. doi: 10.1016/j.cgh.2020.08.065).

HCC, which accounts for most primary liver cancers, generally occurs in patients with several established risk factors, including alcoholic liver disease or nonalcoholic fatty liver disease as well as chronic hepatitis B virus or hepatitis C virus infection. Current guidelines, such as those from the European Association for the Study of the Liver (J Hepatol. 2018 Jul;69[1]:182-236) and those from the American Association for the Study of Liver Diseases (Hepatology. 2018;67[1]:358-80), recommend surveillance of at-risk patients every 6 months by ultrasound with or without AFP measurement. When caught early, HCC is typically treatable and is associated with a higher rate of survival compared with late-stage disease. According to Dr. Chalasani and colleagues, however, the effectiveness of current recommended surveillance for very early stage or early-stage HCC is poor, characterized by a 45% sensitivity for ultrasound and a 63% sensitivity for ultrasound coupled with AFP measurement.

The investigators of the multicenter, case-control study collected blood specimens from 135 patients with HCC as well as 302 age-matched controls with underlying liver disease but no HCC. Very early or early-stage disease was seen in approximately 56.3% of patients with HCC, and intermediate, advanced, or terminal stage disease was seen in 43.7% of patients.

To predict cases of HCC, the re-

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Special immune cell structures could fight cancer

BY BRANDON MAY
MDedge News

In a new study, researchers stimulated immune cells to assemble into tertiary lymphoid structures that improved the efficacy of chemotherapy in a preclinical model of pancreatic cancer.

Overall, the evidence generated by the study supports the notion that induction of tertiary lymphoid structures may potentiate chemotherapy's antitumor activity, at least in a murine model of pancreatic ductal adenocarcinoma (PDAC). A more detailed understanding of tertiary lymphoid structure "kinetics and their induction, owing to multiple host and tumor factors, may help design personalized therapies harnessing the potential of immuno-oncology," Francesca Delvecchio of Queen Mary University of London and colleagues wrote in Cellular and Molecular Gastroenterology and Hepatology (2021 Jul. doi:10.1016/j.jcmgh.2021.06.023).

While the immune system can play a role in combating cancer, a dense stroma surrounds pancreatic cancer cells, often blocking the ability of certain immune cells, such as T cells, from accessing the tumor. As shown by Young and colleagues (Ther Adv Med Oncol. 2018 Dec. doi: 10.1177/1758835918816281), this causes immunotherapies to have very little success in the management of most pancreatic cancers, despite the efficacy of these therapies in other types of cancer.

In some patients with pancreatic cancer, clusters of immune cells can assemble tertiary lymphoid structures within the stroma that surrounds pancreatic cancer. These structures are associated with improved survival in PDAC. In the study, Mr. Delvecchio and colleagues sought to further elucidate the role of tertiary lymphoid structures in PDAC, particularly the structures' antitumor potential.

Clusters of immune cells can assemble tertiary lymphoid structures within the stroma that surrounds pancreatic cancer.

The investigators analyzed donated tissue samples from patients to identify the presence of the structures within chemotherapy-naive human pancreatic cancer. Tertiary lymphoid structures were defined by the presence of tissue zones that were rich in T cells, B cells, and dendritic cells. Staining techniques were used to visualize the various cell types in the samples, revealing tertiary lymphoid structures in approximately 30% of tissue microarrays and 42% of the full section.

Multicolor immunofluorescence and immunohistochemistry were also used to characterize tertiary lymphoid structures in murine models of pancreatic cancer. Additionally, the investigators developed an orthotopic murine model to assess the development of the structures and their role in improving the therapeutic effects of chemotherapy. While tertiary lymphoid structures were not initially present in the preclinical murine model, B cells and T cells subsequently infiltrated into the tumor site following injection of lymphoid chemokines. These cells consequently assembled into the tertiary lymphoid structures.

In addition, the researchers combined chemotherapy gemcitabine with the intratumoral lymphoid chemokine and injected this combination treatment into orthotopic tumors. Following injection, the researchers observed "altered immune cell infiltration," which facilitated the induction of tertiary lymphoid structures and potentiated antitumor activity of the chemotherapy. As a result, there was a significant reduction in the tumors, an effect the researchers did not find following the use of either treatment alone.

According to the investigators, the antitumor activity observed following induction of the tertiary lymphoid structures within the cancer is associated with B cell–mediated activation of dendritic cells, a key cell type involved in initiating an immune response.

Continued on following page

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searchers used a logistic regression algorithm to analyze 10 methylated DNA markers (MDMs) associated with HCC, methylated B3GALT6 (reference DNA marker), and 3 candidate proteins. Finally, the researchers compared the accuracy of the developed blood-based biomarker panel with other blood-based biomarkers – including the GALAD, AFP, AFP-L3, DCP – for the detection of HCC.

The multitarget HCC panel included three MDMs – HOXA1, EMX1, and TSPYL5. In addition, the panel included methylation reference marker B3GALT6 and the protein markers AFP and AFP-L3. The biomarker panel featured a higher sensitivity (71%; 95% confidence interval, 60-81) at 90% specificity for the detection of early-stage HCC compared with the GALAD score (41%; 95% CI, 30-53) or AFP ≥ 7.32 ng/mL (45%; 95% CI, 33-57). The area under the curve for the novel HCC panel for the detection of any stage HCC was 0.92 vs. 0.87 for the GALAD and 0.81 for the AFP measurement alone. The researchers found that the performance of the test was similar between men and women in terms of sensitivity (79% and 84%, respectively). Moreover, the panel performed similarly well among subgroups based on presence of cirrhosis and liver disease etiology.

A potential limitation of this study was the inclusion of controls who were largely confirmed HCC negative by ultrasound, a technique that lacks sensitivity for detecting early-stage HCC, the researchers noted. Given this limitation, the researchers suggest that some of the control participants may have had underlying HCC that was missed by ultrasound. Furthermore, the findings indicate that the cross-sectional nature of the study may also mean some of the control participants had HCCs that were undetectable at initial screening.

Despite the limitations of the study, the researchers reported that the novel, blood-based marker panel's sensitivity for detecting early-stage HCC likely supports its use "among at-risk patients to enhance HCC surveillance and improve early cancer detection."

The study was funded by the Exact Sciences Corporation. The researchers reported conflicts of interest with several pharmaceutical companies.

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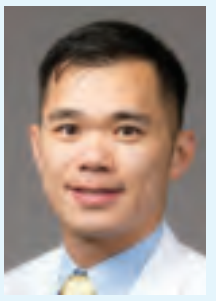
Hepatocellular carcinoma (HCC) is frequently diagnosed at late stages, leading to a high mortality rate given the limited treatment options. One of the major barriers to early diagnosis of HCC is the suboptimal sensitivity of the current diagnostic modality. Most recently, liquid biopsy has been used to diagnose and prognosticate various tumors, including HCC.



Dr. Lee

In this study, Dr. Chalasani and colleagues developed a biomarker panel consisting of three methylated DNA markers, methylated B3GALT6 (reference DNA marker) and two proteins (AFP and AFP-L3), to diagnose HCC. This panel demonstrated higher sensitivity (71%) at 90% specificity for early-stage HCC than the GALAD score (41%) or AFP (45%). It is exciting news for clinicians since this novel blood-based test could identify patients who are qualified for curative HCC treatment without the limitations of image-based tests such as body habitus or renal function. Although the cohort is relatively small, the performance is equally good in subgroups of patients based on liver disease etiology, presence of cirrhosis, or sex. We are looking forward to seeing the validation data of this biomarker panel in larger independent cohorts and the studies that compare this panel to abdominal ultrasound, which is the most commonly used tool for HCC surveillance. Hopefully, the sensitivity of the biomarkers-based tests can be further increased, and the costs can be lowered in the near future with more studies in this field. A powerful and cost-effective biomarker-based test that can either replace or enhance current HCC surveillance tools will bring tremendous benefits to our patients.

Howard T. Lee, MD, is with the department of hepatology at Baylor College of Medicine, Houston. He has no relevant conflicts of interest.

Updated MELD score adds serum albumin, female sex

BY BRANDON MAY
MDedge News

A newly updated version of the Model for End-Stage Liver Disease (MELD) score was effective for predicting short-term mortality in patients with end-stage liver disease and addressed important determinants of wait-list outcomes that haven't been addressed in previous versions, according to findings from a recent study. The new model, termed MELD 3.0, includes new variables such as female sex, serum albumin, and updated creatinine cutoffs.

"We believe that the new model represents an opportunity to lower wait-list mortality in the United States and propose it to be considered to replace the current version of MELD in determining allocation priorities in liver transplantation," wrote study authors W. Ray Kim, MD, of Stanford (Calif.) University and colleagues in Gastroenterology (2021 Sep. 2021. doi: 10.1053/j.gastro.2021.08.050).

In patients with end-stage liver disease, the MELD score was shown to be a reliable predictor of short-term survival, according to the researchers. The original version of MELD consists of international normalized ratio of prothrombin time and serum concentrations of bilirubin and creatinine; MELDNa consists of the same with the addition of serum concentrations of total sodium. Since 2016, MELDNa has been utilized in the United States to allocate livers for transplant.

Despite the utility of the current MELD score, questions have been raised concerning the accuracy of the tool's ability to predict mortality, including a study by Sumeet K. Asrani, MD, MSc, and colleagues (Hepatology. 2020;71(5):1766-74). Changes in liver disease epidemiology, the introduction of newer therapies that alter prognosis, as well as increasing age and prevalence of comorbidities in transplant-eligible patients, are several drivers for these concerns, according to Dr. Kim and colleagues. Also, there is an increasing concern regarding women and their potential disadvantages in the current system: At least one study has suggested that serum creatinine may overestimate renal function

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Introduction of the Model for End-Stage Liver Disease (MELD) score in 2002, consisting of objective measurements of creatinine, bilirubin, and international normalized ratio, revolutionized liver allocation in the United States. To minimize patient wait-list mortality and reduce geographic variability, further improvements to allocation system including the National Share for status 1 and Regional Share for MELD score greater than 35 in 2013, adoption of MELDNa score in 2016, and most recently the introduction of the Acuity Circles distribution system were implemented. Unfortunately, MELD tends to disadvantage women whose lower muscle mass translates to lower normal creatinine levels, thereby underestimating the degree of renal dysfunction and wait-list mortality. MELD performance characteristics were also shown to be less accurate in patients with alcoholic and nonalcoholic fatty liver disease when compared with patients with hepatitis C, likely contributing to MELD's decreasing accuracy in predicting mortality over the years with changing patient population.


Dr. Shingina

To address these deficiencies, the study by Kim and colleagues explores a new iteration of organ prioritization system – MELD 3.0 – which includes adjustments for gender and albumin level, and lowering the upper limit of creatinine to 3.0 mg/dL (from 4.0 mg/dL) with validation in a contemporary cohort of listed patients. Undoubtedly, this is a step in the right direction for gender equity in organ allocation as well more accurate assessment of renal dysfunction. The incorporation of albumin into the model is more controversial. The indications for albumin administration ranges from large volume paracentesis to volume expansion for many admitted patients and is more likely to occur in patients with worse liver disease. The risks and benefits of such a volatile component will need to be carefully weighed before implementation. MELD 3.0 holds promise in bringing equity to liver organ allocation as well as improving wait-list mortality, and we are likely to see MELD 3.0 (or a variation thereof) dominate the field in the near future.

Alexandra Shingina, MD, MSc, is an assistant professor of medicine in the division of gastroenterology, hepatology, and nutrition at Vanderbilt University Medical Center, Nashville, Tenn. She has no relevant conflicts of interest.

Continued from previous page

Based on the findings, the researchers concluded that the combination of chemotherapy and lymphoid chemokines might be a viable strategy for promoting an antitumor immune response in pancreatic cancer. In turn, the researchers suggest this strategy may result in better clinical outcomes for patients with the disease. Additionally, the researchers wrote that mature tertiary lymphoid structures in PDAC prior to an immune treatment could "be used as a biomarker to define inclusion criteria of patients in immunotherapy protocols, with the aim to boost the ongoing antitumor immune response."

The study relied on a mouse model and for this reason, it remains unclear at this time if the findings will be generalizable to humans. In the context of PDAC, the researchers wrote that further investigation and understanding of the formation of tertiary lymphoid structures may support the development of tailored treatments, including those that take advantage of the body's immune system, to combat cancer and improve patient outcomes.

The researchers reported no conflicts of interest with the pharmaceutical industry. No funding was reported for the study.

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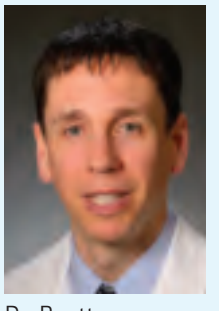
Pancreatic ductal adenocarcinoma (PDAC) is known for its remarkable resistance to immunotherapy. This observation is largely attributed to the microenvironment that surrounds PDAC due to its undisputed role in suppressing and excluding T cells – key mediators of productive cancer immune surveillance. This study by Delvecchio and colleagues now examines the formation and maturation of tertiary lymphoid structures (TLS) – highly organized immune cell communities – that can be found within murine and human PDAC tumors and correlate with a favorable prognosis after surgical resection in patients. Intriguingly, the authors show that intratumoral injection of lymphoid chemokines (CXCL13/CCL21) can trigger TLS formation in murine PDAC models and potentiate the activity of chemotherapy. Notably, in other solid cancers, the presence of mature TLS has been associated with response to immunotherapy, raising the possibility that inciting TLS formation and maturation in PDAC may be a first step toward overcoming immune resistance in this lethal cancer. Still, much work is needed to understand mechanisms by which TLS influence PDAC biology and how to effectively deliver drugs to stimulate TLS beyond intratumoral injection, which is less practical given the highly metastatic proclivity of PDAC. Nonetheless, TLS hold promise as a therapeutic target in PDAC and may even serve as a novel biomarker of treatment response.


Dr. Beatty

Gregory L. Beatty, MD, PhD, is director of the Clinical and Translational Research Program for Pancreas Cancer at the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, and associate professor in the department of medicine in the division of hematology/oncology at the University of Pennsylvania. He reports involvement with many pharmaceutical companies, as well as being the inventor of certain intellectual property and receiving royalties related to CAR T cells.

A letter from Robert S. Sandler, MD, MPH, AGAF, chair of the AGA Research Foundation

Dear AGA members,
Please remember the AGA Research Foundation in your year-end charitable giving.

During these trying times, there is one thing that hasn't and won't change – our commitment to our mission to raise funds to support young researchers in GI and hepatology.

Real progress in the diagnosis, treatment, and cure of digestive disease is possible through research. A growing and diverse research community is critical to our field and our patients.

You understand the value of research to advance patient care; that's why I'm asking for your help.

The AGA Research Foundation was able to award 45 investigators with research funding in the 2021 award year. Despite this success, more than 115 other innovative and promising research ideas went unfunded. Donations will help the AGA Research Foundation continue to foster the careers of researchers.

Research funding from traditional sources, like National Institutes of Health, is shrinking, and even greater cuts may be on the horizon. Every dollar is a step forward in helping to spark the scientific breakthroughs of today so clinicians will have the tools to improve care tomorrow.

You can help with a special year-end gift to support our efforts to fund GI research. Donate today at http://www.gastro.org/giveonline2. Be sure to give your special year-end donation by Dec. 31 to receive a tax credit this year.

Best wishes for a safe and healthy holiday season!

Take action: Medicare rules

2022 Medicare payment rules contain both good and bad news for GI. First the bad news: GIs and other specialties face millions of dollars in cuts as Medicare finalized a 3.71% cut to the Physician Fee Schedule conversion factor, which could increase to near 9% if Congress doesn't act.

Here are highlights from the 2022 Medicare Physician Fee Schedule (MPFS) and Hospital Outpatient Department (HOPD)/Ambulatory Surgery Center (ASC) final rules.

Good news

- Telehealth reimbursement continues through December 2023.
- Medicare coverage changes from the Removing Barriers to Colorectal Cancer Screening Act were finalized, and coinsurance reduction will start Jan. 1, 2022, with full phase out by 2030.

Bad news

- A 3.71% cut to MPFS 2022 conversion factor, which could result in an up to 9% cut to our practices. Email your lawmakers now.
- HOPD and ASC conversion factors will increase 2% for those that meet applicable quality reporting requirements.
- New MPFS payments for peroral endoscopic myotomy (POEM) and some capsule endoscopy CPT codes not as high as expected.

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and consequently underestimate mortality risk in female patients, compared with men with the same creatinine level (Transplantation. 2018;102[10]:1710-6).

Dr. Kim and colleagues sought to further optimize the fit of the current MELD score by considering alternative interactions and including other variables relevant to predicting short-term mortality in patients awaiting liver transplant. The study included patients who are registered on the Organ Procurement and Transplantation Network Standard Transplant Analysis and Research files newly wait-listed from 2016 through 2018. The full cohort was divided 70:30 into a development set (n = 20,587) and a validation set (n = 8,823); there were no significant differences between the sets in respect to age, sex, race, or liver disease severity.

The investigators used univariable and multivariable regression models to predict 90-day survival following wait-list registration. Additionally, model fit was tested, and the investigators used the Liver Simulated Allocation Model to estimate the impact of replacing the current version of the MELD with MELD 3.0.

Sebastian Kaulitzki/Thinkstock

In the final MELD 3.0 model, the researchers included several additional variables such as female sex and serum albumin. Additionally, the final model was characterized by interactions between bilirubin and sodium as well as between albumin and creatinine. Also, an adjustment to the current version of MELD lowered the upper bound for creatinine from 4.0 mg/dL to 3.0 mg/dL.

The MELD 3.0 featured significantly better discrimination, compared with the MELDNa (C-statistic = 0.8693 vs. 0.8622, respectively; $P < .01$). In addition, the researchers wrote that the new MELD 3.0 score "correctly reclassified a net of 8.8% of decedents to a higher MELD tier, affording them a meaningfully higher chance of transplantation, particularly in women." The MELD 3.0 score with albumin also led to fewer wait-list deaths, compared with the MELDNa, according to the Liver Simulated Allocation Model analysis ($P = .02$); the number for MELD 3.0 without albumin was not statistically significant.

According to the investigators, a cause of concern for the MELD 3.0 was the addition of albumin, as this variable may be vulnerable to manipulation. In addition, the researchers note that, while differences in wait-list mortality and survival based on race/ethnicity were observed in the study, they were unable to describe the exact root causes of worse outcomes among patients belonging to minority groups. "Thus, inclusion in a risk prediction score without fully understanding the underlying reasons for the racial disparity may have unintended consequences," the researchers wrote.

"Based on recent data consisting of liver transplant candidates in the United States, we identify additional variables that are meaningfully associated with short-term mortality, including female sex and serum albumin. We also found evidence to support lowering the serum creatinine ceiling to 3 mg/dL," they wrote. "Based on these data, we created an updated version of the MELD score, which improves mortality prediction compared to the current MELDNa model, including the recognition of female sex as a risk factor for death."

The researchers reported no conflicts of interest with the pharmaceutical industry. No funding was reported for the study.

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GI & Hepatology News: A new team onboarded


Dr. Adams


Dr. Gellad


Dr. Jou


Dr. Katzka


Dr. Ketwaroo


Dr. Kochar


Dr. Persley


Dr. Rosenberg

This fall, GI & Hepatology News welcomed its new board of editors, which was assembled by the new Editor in Chief, Dr. Adams, and the American Gastroenterological Association, and will serve for the next 5 years. Together they will oversee and guide the publication as it continues to bring readers important, clinically relevant news.

Megan A. Adams, MD, JD, MSc

Dr. Adams is a general gastroenterologist, attorney, and health services researcher. She is assistant professor of medicine in the division of gastroenterology at the University of Michigan, Ann Arbor; a member of the core faculty of the University of Michigan Gastroenterology Clinical T32 Fellowship Training Program; and an investigator in the University of Michigan Institute for Healthcare Policy and Innovation and Ann Arbor VA Center for Clinical Management Research. Her work focuses primarily on optimizing specialty care access and delivery by helping to define, measure, and implement high-value care across diverse practice settings. She also frequently contributes commentaries on important clinical practice and health law topics affecting frontline GI policy and practice. She served as chair of the AGA Quality Committee (2017-2020), member of the AGA Nominating Committee (2020), Associate Editor of GI & Hepatology News (2016-2021), and current Chair of the AGA Audit and Ethics Committees (2021-2024).

Ziad F. Gellad, MD, MPH, AGAF

Dr. Gellad is associate professor of medicine in the division of gastroenterology at Duke University Medical Center in Durham, N.C., and a practicing clinician with a focus in esophageal disease. He is the director of quality for the division of gastroenterology and associate vice chair for ambulatory services in the department of medicine. Dr. Gellad received his MD and MPH degrees from Johns Hopkins University, Baltimore, and completed a residency in internal medicine and a fellowship in gastroenterology at Duke University Medical Center. Dr. Gellad has received several innovation grants to develop and implement novel information technology platforms to improve the patient and clinician experience. He is also an active contributor to the innovation and entrepreneurship activities within Duke University and cofounder of a health technology startup in Durham.

Janice H. Jou, MD, MHS

Dr. Jou is a transplant hepatologist and GI section chief at the VA Portland Healthcare System and associate professor in the division of gastroenterology and hepatology at Oregon Health & Science University, also in Portland. Dr. Jou is the program director for the gastroenterology fellowship at OHSU and is actively involved in leading educational activities for the American Association for the Study of Liver Diseases and the AGA. Her research interests include outcomes for hepatocellular carcinoma and processes of care in chronic liver disease.

David Katzka, MD, AGAF

Dr. Katzka has had a career-long clinical interest in diseases of the esophagus. A professor of medicine at the Mayo Clinic, Rochester, Minn., he works as part of a team publishing articles on all areas of esophagology including Barrett's esophagus, esophageal adenocarcinoma, esophageal motility disorders, eosinophilic esophagitis, and rare esophageal diseases. He has had the privilege of serving on editorial boards for many of the high-impact journals in gastroenterology and has had multiple positions in the AGA for education and clinical practice.

Gyanprakash A. Ketwaroo, MD, MSc

Dr. Ketwaroo is assistant professor and director of quality improvement in the division of gastroenterology and hepatology at Baylor College of Medicine and director of advanced endoscopy at the Michael E. Debakey VA Medical Center, both in Houston. After graduating with a degree in chemical physics from Brown University, Providence, R.I., he studied at Oxford (England) University on a Rhodes Scholarship. He attended Harvard Medical School and completed an internal medicine residency at Massachusetts General Hospital, both in Boston. This was followed by gastroenterology and advanced endoscopy fellowship training at Beth Israel Deaconess Medical Center, also in Boston. He is a member of the AGA Quality and Publication Committees. His research interests include Barrett's esophagus, chronic pancreatitis, and advanced imaging of gastrointestinal disease.

Bharati Kochar, MD, MS

Dr. Kochar is a gastroenterologist and inflammatory bowel disease specialist at Massachusetts General Hospital and a physician investigator in the clinical and translational epidemiology unit at The Mongan Institute, both in Boston. She attended college and medical school at Brown University, Providence, R.I.; trained in internal medicine at Johns Hopkins Hospital in Baltimore; and completed a fellowship in GI and hepatology as well as an advanced fellowship in IBD at the University of North Carolina, Chapel Hill, where she obtained an MS in clinical research. Dr. Kochar's clinical interests include underserved and understudied patients with IBD. She completed a career development award from the Crohn's and Colitis Foundation to report the pharmacoepidemiology of biologic agents in older adults with IBD. Dr. Kochar was part of the AGA Future Leaders Program and previously served on the Quality Committee.

Kimberly M. Persley, MD, AGAF

Dr. Persley graduated from Texas Wesleyan University with a BS in Biology in 1989, then from the University of Texas Southwestern Medical School in 1993. She completed her internship and residency and chief residency in internal medicine at UTSW; she completed her gastroenterology fellowship training in the June 1999 at UTSW. She did additional study in inflammatory bowel disease at Mount Sinai Medical Center in New York in 2001. She is a partner with Texas Digestive Disease Consultants in Dallas and has been on the medical staff of Texas Health Presbyterian Hospital since 2001. She currently serves on the Peer Evaluation Committee. Dr. Persley is actively involved in several professional organizations and has served on several AGA committees including Education & Training, Quality Measures, and women's committees. Dr. Persley is the recipient of several awards including the Crohn's and Colitis North Texas Chapter Physician of the year 2020, AGA Distinguished Clinician Award in Private Practice 2020, and Texas Wesleyan University Medal Award 2020 Distinguished Alumni.

Jonathan Rosenberg, MD, AGAF

Dr. Rosenberg is a partner in the Illinois Gastroenterology Group, which is a platform practice of the GI Alliance – the largest independent practice in the United States. He received his medical degree from the University of Illinois College of Medicine and completed his internship and residency in internal medicine at the University of Illinois Medical Center in Chicago. He then completed his fellowship training in gastroenterology at the University of Chicago, followed by an advanced therapeutic endoscopy fellowship at the University of Illinois Medical Center. Dr. Rosenberg is the medical director of research for the Illinois Gastroenterology Group and serves on the medical advisory board for the GI Alliance. He currently is involved in the AGA's Quality Leadership Council and Clinical Advisory Network. He has served on the Nominating Committee and the Government Affairs Committee. Dr. Rosenberg is a graduate of the AGA Future Leaders program.

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AGA Clinical Practice Guideline

Management of coagulation concerns in cirrhosis

BY JIM KLING
MDedge News

A clinical update from the American Gastroenterological Association focuses on bleeding and thrombosis-related questions in patients with cirrhosis. It provides guidance on test strategies for bleeding risk, preprocedure management of bleeding risk, venous thromboembolism (VTE) prophylaxis, screening for portal vein thrombosis (PVT), and anticoagulation therapies. It is aimed at primary care providers, gastroenterologists, and hepatologists, among other health care providers.

In cirrhosis, there are often changes to platelet (PLT) counts and prothrombin time/international normalized ratio (PT/INR), among other parameters, and historically these changes led to concerns that patients were at greater risk of bleeding or thrombosis. More recent evidence has led to a nuanced view. Neither factor necessarily suggests increased bleeding risk, and the severity of coagulopathy predicted by them does not predict the risk of bleeding complications.

Patients with cirrhosis are at greater risk of thrombosis, but clinicians may be hesitant to prescribe anticoagulants because of uncertain risk profiles, and test strategies employing PT/INR to estimate bleeding risk and track treatment endpoints in patients receiving vitamin K antagonists may not work in cirrhosis patients with alterations in procoagulant and anticoagulant measures. Recent efforts to address this led to testing of fibrin clot formation and lysis to better gauge the variety of abnormalities in cirrhosis patients.

The guideline, published in Gastroenterology (2021 Nov;161[5]:1615-27.e1), was informed by a technical review that focused on both bleeding-related and thrombosis-related questions. Bleeding-related questions included testing strategies and preprocedure prophylaxis to reduce bleeding risk. Thrombosis-related questions included whether VTE prophylaxis may be useful in hospitalized patients with cirrhosis, whether patients should be screened for PVT, potential therapies for nontumoral PVT, and whether or not anticoagulation is safe and effective when atrial fibrillation is present alongside cirrhosis.

Because of a lack of evidence, the guideline provides no recommendations on visco-elastic testing for bleeding risk in advance of common gastrointestinal procedures for patients with stable cirrhosis. It recommends against use of extensive preprocedural testing, such as repeated PT/INR or PLT count testing.

The guideline also looked at whether preprocedural efforts to correct coagulation parameters could reduce bleeding risk in patients with cirrhosis. It recommends against giving blood products ahead of the procedure for patients with stable cirrhosis without severe thrombocytopenia or severe coagulopathy. Such interventions can be considered for patients in the latter categories who are undergoing procedures with high bleeding risk after consideration of risks and benefits, and consultation with a hematologist.

Thrombopoietin receptor agonists (TPO-RAs) are also not recommended in patients with thrombocytopenia and stable cirrhosis undergoing common procedures, but they can be considered for patients who are more concerned about reduction of bleeding events and less concerned about the risk of PVT.

Patients who are hospitalized and meet the requirements should receive VTE prophylaxis. Although there is little available evidence about the effects of thromboprophylaxis in patients with cirrhosis, there is strong evidence of benefit in acutely ill hospitalized patients, and patients with cirrhosis are believed to be at a similar risk of VTE. There is evidence of increased bleed risk, but this is of very low certainty.

PVT should not be routinely tested for, but such testing can be offered to patients with a high level of concern over PVT and are not as worried about potential harms of treatment. This recommendation does not apply to patients waiting for a liver transplant.

Patients with non-tumoral PVT should receive anticoagulation therapy, but patients who have high levels of concern about bleeding risk from anticoagulation and put a lower value on possible benefits of anticoagulation may choose not to receive it.

The guideline recommends anticoagulation for patients with atrial fibrillation and cirrhosis who are indicated for it. Patients with more concern about the bleeding risk of anticoagulation and who place lower value on the reduction in stroke risk may choose to not receive anticoagulation. This is particularly true for those with more advanced cirrhosis (Child-Turcotte-Pugh Class C) and/or low CHA2DS2-VASC scores.

Nearly all of the recommendations in the guideline are conditional, reflecting a lack of data and a range of knowledge gaps that need filling. The authors call for additional research to identify specific patients who are at high risk for bleeding or thrombosis "to appropriately provide prophylaxis using blood product transfusion or TPO-RAs in patients at risk for clinically significant bleeding, to screen for and treat PVT, and to prevent clinically significant thromboembolic events."

The development of the guideline was funded fully by the AGA. Members of the panel submitted conflict of interest information, and these statements are maintained at AGA headquarters.

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AGA Clinical Care Pathway

Screening, diagnosis, and treatment of NAFLD and NASH

BY WILL PASS
MDedge News

The American Gastroenterological Association recently published a Clinical Care Pathway for screening, diagnosis, and treatment of patients with nonalcoholic fatty liver disease (NAFLD).

Recommendations are intended for a spectrum of clinical settings, including primary care, obesity medicine, gastroenterology, hepatology, and endocrinology practices, reported lead author Fasiha Kanwal, MD, AGAF, of Baylor College of Medicine, Houston, and colleagues.

"Most patients with NAFLD and NASH [nonalcoholic steatohepatitis] are seen in primary care or endocrine clinics," the authors wrote in Gastroenterology (2021 Sep. doi: 10.1053/j.gastro.2021.07.049). "Although not all patients with NAFLD/NASH require secondary (i.e., hepatology) care, not knowing which patients might benefit from such care and when to refer them results in inconsistent care processes and possibly poor outcomes. Clinical Care Pathways, with careful explication of each step in screening, diagnosis, and treatment, have been shown to improve the quality of health care delivery in other areas of medicine, [and] are crucial to addressing the often inconsistent care processes characterizing current approaches to NAFLD/NASH."

The guidance was drafted by a group of 15 multidisciplinary experts from around the world representing the AGA, the American Diabetes Association, the American Osteopathic Association,

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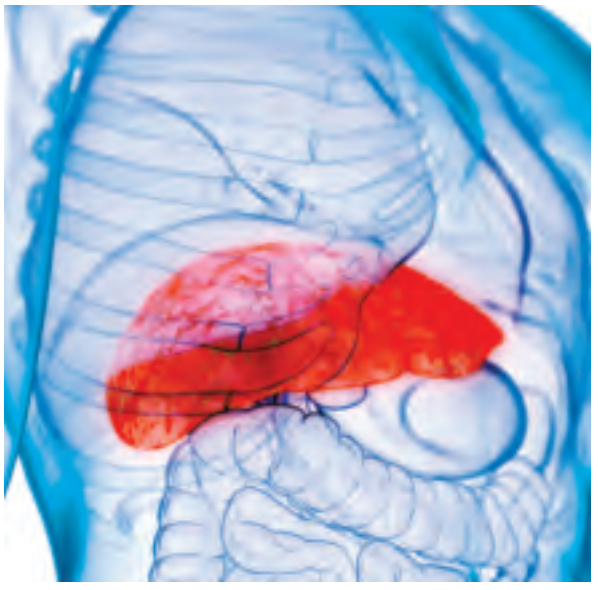

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Maraviroc fails to control NAFLD in people with HIV

BY HEATHER BOERNER

The MAVMET study, the first randomized controlled trial of maraviroc (Selzentry) with or without metformin, failed to reduce liver fat in people living with HIV and nonalcoholic fatty liver disease compared with placebo – and in some cases, prolonged use actually increased liver fat.

And that means clinicians like Yvonne Gilleece, MB BCh, who was not involved in the study but does run a liver clinic in England for people living with HIV, are returning to the one intervention proven to work. "As yet, the only thing that is proven to have a very positive effect that is published is weight loss," said Dr. Gilleece, who runs the clinic at Brighton and Sussex University Hospital. "You don't put someone on these particular drugs, particularly this combination, easily. MAVMET has really demonstrated that, actually, it's not effective, and it's not particularly beneficial to patients."

The MAVMET trial data were presented at the 18th European AIDS Conference,

There was good reason to think maraviroc might work. A 2018 study in the journal Hepatology found that one of maraviroc's molecular cousins, cenicriviroc, significantly reduced fibrosis in people with NAFLD. Dr. Gilleece is co-investigator of another study of maraviroc in NAFLD, the HEPMARC trial, which is wrapping up now. In addition to those studies, there are other potential treatments in ongoing trials, including semaglutide, which is being studied in the United States under the study name SLIM LIVER.

MAVMET enrolled 90 people living with HIV from six clinical sites in London who were 35 or older and who had at least one marker for NAFLD, such as abnormal liver lab results. But 70% qualified via imaging- and/or biopsy-confirmed NAFLD. Almost all participants (93%) were men and 81% were White. The trial excluded people who were pregnant or breastfeeding. The median age was 52, and the participants met the criteria for overweight but not obesity, with a median BMI of 28.

In other words, participants generally had fatty livers without the inflammation that characterizes the more aggressive nonalcoholic steatohepatitis (NASH). Clinicians can't yet differentiate between those who will continue to have asymptomatic fatty liver and those who will progress to NASH and potentially need a liver transplant.

All people living with HIV in the trial had undetectable viral loads and were on HIV treatment. Nearly 1 in 5 (19%) were using a treatment regimen containing tenofovir alafenamide (TAF), which has been associated with weight gain. Nearly half were on integrase strand inhibitors.

Investigators divided the participants into four groups: 24 people stayed on their HIV treatment and added nothing else; 23 people took maraviroc only; 21 took metformin only; and the final group took both maraviroc and metformin. Across groups, liver fat at baseline was 8.9%, and 78% had mild hepatic steatosis.

After taking the medications for 48 weeks, participants returned to the clinic to be scanned via MRI proton density fat fraction (MRI-PDFF), which has been found to successfully measure liver fat. However, because of the COVID-19 pandemic, 20 of the 83 people who returned to the clinic came later than 48 weeks after the trial began.

When investigators looked at the results, they didn't see what

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the Obesity Society, and the Endocrine Society. Recommendations were based on available literature and clinical experience.

The authors recommended a four-step screening process for NAFLD/NASH: Check for risk factors predicting clinically relevant fibrosis (stage F2 or higher), review history and perform relevant laboratory tests, conduct noninvasive liver fibrosis testing, and measure liver stiffness.

"Clinical Care Pathways, with careful explication of each step in screening, diagnosis, and treatment, have been shown to improve the quality of health care delivery in other areas of medicine."

Patients at greatest risk for clinically significant fibrosis include those with two or more metabolic risk factors, those with type 2 diabetes, and those with incidentally detected steatosis and/or elevated aminotransferases.

"A recent retrospective cohort study [Hepatology. 2020 Oct;72(4):1242-52] found that patients with hepatic steatosis and elevated alanine aminotransferase had a significantly higher risk of progression to cirrhosis or hepatocellular carcinoma than patients with hepatic steatosis and persistently normal alanine aminotransferase," the authors noted.

When any of the above risk factors are present, the authors recommended checking the patient's history for excessive alcohol intake, conducting a complete blood count and liver function tests, and screening for other hepatic and biliary diseases, such as chronic hepatitis C virus infection and liver mass lesions.

If other liver diseases have been ruled out, the first step in liver fibrosis risk stratification involves noninvasive testing, with the authors favoring the Fibrosis-4 (FIB-4) score "because it has been shown to have the best diagnostic accuracy for advanced fibrosis, compared with other noninvasive markers of fibrosis in patients with NAFLD."

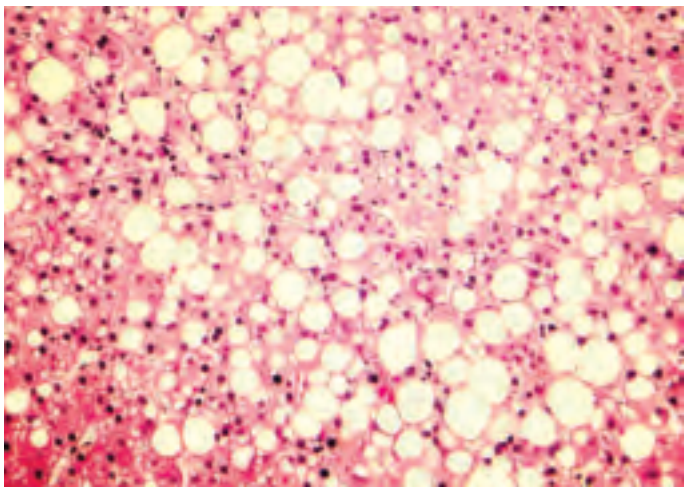
Dr. Kanwal

The next step in risk stratification involves liver stiffness measurement (LSM) with FibroScan (vibration controlled transient elastography [VCTE]), or newer modalities, such as bidimensional shear wave elastography or point shear wave elastography, which offer "diagnostic performances at least as good as VCTE."

According to the publication, patients with NAFLD at low risk of advanced fibrosis (FIB-4 less than 1.3 or LSM less than 8 kPa or liver biopsy F0-F1) can be managed by one provider, such as a primary care provider or endocrinologist, whereas indeterminate-risk patients (FIB-4 of 1.3-2.67 and/or LSM 8-12 kPa and liver biopsy unavailable) and high-risk patients (FIB-4 greater than 2.67 or LSM greater than 12 kPa or liver biopsy F2-F4) should be managed by a multidisciplinary team led by a hepatologist.

Lifestyle intervention, weight loss (if overweight or obese), and cardiovascular disease risk reduction are advised for patients of all risk categories.

"There are no large, long-term behavioral modification or pharmacotherapy studies regarding weight loss in individuals with NAFLD," the authors wrote. "However, weight loss of any magnitude should be encouraged as beneficial."



DR_MICROBE/ISTOCK/GETTY IMAGE

For patients with indeterminate and high risk, NASH pharmacotherapy is recommended, and if needed, diabetes care should involve medications with efficacy in NASH, such as pioglitazone.

"Although we recognize that knowledge is continuing to evolve and that recommendations may change accordingly over time, we believe this Pathway provides accessible, standardized, evidence-based, timely, and testable recommendations that will allow clinicians to care for a rapidly growing population of patients, most of whom are managed in primary care or endocrine clinics," the authors concluded.

The article was supported by the American Gastroenterological Association, Intercept Pharmaceuticals, Pfizer, and others. The authors disclosed relationships with Novo Nordisk, Eli Lilly, Sanofi, and others.

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Continued from previous page

they hypothesized, said Sarah Pett, MBBS, professor of infectious diseases at University College London: The scatter plot graph of change in weight looked, well, scattershot: People who didn't take any additional treatment sometimes lost more liver fat than those on treatment. In fact, the mean liver fat percentage rose by 2.2% in the maraviroc group, 1.3% in the metformin group, and 0.8% in the combination group. The control group saw an increase of 1.4% – meaning that there was no difference in the change in fat between those on treatment and those not.

What's more, those who had delayed scans – and stayed on their treatment for a median of an additional 16 weeks – saw their liver fat increase even more.

In an interview, Dr. Pett called the results "disappointing." "The numbers are quite small, but we still didn't expect this," she said. "It's not explained by lockdown weight gain, although we still have to look in detail at how alcohol consumption could have contributed."

There were also some limits to what the design of this particular trial could tell the researchers. For instance, nearly half of the participants in the maraviroc group, a third of the people in the metformin group, and 36% of those in the combination group had hepatic steatosis grades of 0, meaning that their livers were healthy. And MRI-PDFF becomes less reliable at that level.

"One of the regrets is that perhaps we should have done FibroScan [ultrasound], as well," Dr. Pett said. The consequence is that the study may have undercounted the fat level by using MRI-PFDD.

"This suggests that the surrogate markers of NAFLD used in MAVMET were not very sensitive to those with a higher percentage of fat," Dr. Pett said during her presentation. "We were really trying to be pragmatic and not require an MRI at screening."

Whatever the case, she said that the failure of this particular treatment just highlights the growing need to look more seriously, and more collaboratively, at fat and liver health in people living with HIV.

"We need to really focus on setting up large cohorts of people living with HIV to look in a rigorous way at weight gain ... to acquire some longitudinal data."

"We need to really focus on setting up large cohorts of people living with HIV to look in a rigorous way at weight gain, changes in waist circumference, ectopic fat, capture fatty liver disease index scores, and cardiovascular risk, to acquire some longitudinal data," she said. "And [we need to] join with our fellow researchers in overweight and obesity medicine and hepatology to make sure that people living with HIV are included in new treatments for NASH, as several large RCTs have excluded [people living with HIV]."

From Dr. Gilleece's perspective, it also just speaks to how far the field has to go in identifying those with asymptomatic fatty livers from those who will progress to fibrosis and potentially need liver transplants.

"MAVMET shows the difficulty in managing NAFLD," she said. "It seems quite an innocuous disease, because for the majority of people it's not going to cause a problem in their lifetime. But the reality is, for some it will, and we don't really know how to treat it."

Dr. Gilleece has disclosed no relevant financial relationships. Dr. Pett reported receiving funding for trials from Gilead Sciences and Janssen-Cilag. ViiV Healthcare funded the MAVMET trial.

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No effect seen with decaf

Coffee *from page 1*

detail, the granularity, the richness of the information from the nutritional surveys that they do, this is the closest we're ever going to get to a linkage between what people are eating or drinking and the health of their liver, absent a longitudinal study where we set out to follow people for many, many years," said Elliot Tapper, MD, assistant professor of gastroenterology at the University of Michigan, Ann Arbor, and the study's senior author.

Researchers examined data from about 4,500 patients who had participated in the NHANES study in 2017-2018. The participants were aged 20 years or older, with an average age of 48; 73% were overweight, about the national average.

The researchers found no association between coffee consumption and controlled attenuation parameter (CAP), a measure of fatty liver. But they found a link between coffee and liver stiffness.

Those who drank more than three cups of coffee daily had a liver stiffness measure (LSM) that was 0.9 kilopascals (kPa) lower than others (P = .03). Furthermore, drinking more than three cups a day also was found to be protective against an LSM of 9.5 kPa or higher, the threshold for advanced liver fibrosis (OR, 0.4; P = .05). Decaffeinated coffee was not found to be associated with LSM.

Caffeine is an antagonist to adenosine receptors in the liver cell that, if blocked, stops the production of scar tissue, according to the researchers. But when they looked at estimated caffeine consumption, calculated through the detailed, trained interviews performed by nutritionists, there was no association with liver stiffness. That said, Dr. Tapper noted that this could be due to the imperfection of making those estimations.

"For patients who are very interested in a natural supplement, to feel like they're taking an active role in the health of their liver, I will tell them to avoid carbohydrates and increase their exercise – and that it is OK to add coffee to their daily routine."

"If we had to hypothesize about a mechanism, it would most likely be caffeine, and the reason we couldn't see that here is because these are estimated milligrams of caffeine per coffee – but the way that we brew coffee, and the beans that we're using, are so highly variable it just can't be captured in this kind of database," he said.

He said the data will be reassuring to clinicians who suggest coffee-drinking to patients.

"There are hepatologists around the world who are actively recommending coffee – they'll feel empowered by these data," he said. "I would still like to see more robust longitudinal data before I start spending our precious time counseling patients about coffee. There are many other data-driven interventions for the management of liver disease that we should be focusing our time on."

Moreover, he said that the data will be important for patients who are particularly interested in natural remedies.

"For patients who are very interested in a natural supplement, to feel like they're taking an active role in the health of their liver, I will tell them to avoid carbohydrates and increase their exercise – and that it is OK to add coffee to their daily routine."

A study based on a U.K. database (BMC Public Health. 2021 Jun 22;21[1]:970) found that coffee was associated with protection against chronic liver disease, but the association was seen for both caffeinated and decaffeinated drinks, noted Nathan Davies, PhD, professor of biochemistry at the Institute of the Liver and Digestive Health at the University College London.

Dr. Davies, a registered nutritionist who has studied coffee's effects on the liver, said that while including elastography in the Michigan study is interesting, it "does not necessarily by itself add greatly" to the evidence base.

The outcomes from both studies do suggest a positive effect for coffee, but he said it's important to remember that liver disease develops over years and decades.

"Looking at a snapshot moment does not necessarily reflect an individual's behavior during the onset and development of their condition," he said. "As such, there are a number of behavioral and nutritional factors that could be contributing to the observed effect over a period of years."

He pointed out that while different coffee and brewing types affect the amount of caffeine in a cup, all cups of coffee in this study were treated the same way. He noted there was no apparent dose-dependent effect, which would have been expected if there is an active ingredient that affects liver stiffness.

"In general, my advice is to improve diet, take more exercise, and reduce alcohol consumption, which is likely to be more effective in preventing liver disease – and its progression – than drinking an extra cup of coffee," Dr. Davies said. "That being said, for patients at increased risk for liver disease who currently drink three cups or more of coffee daily, it may be prudent for them to continue because this level of consumption might be actively lowering their chances of developing more serious disease."

Dr. Tapper has done consulting for Novartis, Axcella, and Allergan, has served on advisory boards for Mallinckrodt, Bausch Health, Kaleido, and Novo Nordisk, and has unrestricted research grants from Gilead and Valeant. The remaining authors disclose no conflicts. Dr. Davies reported no relevant disclosures.

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DDSEP 9

Quick quiz

Q1. A 36-year-old man presents to the clinic with a history of diarrhea and significant fatigue for the last 2 months. He has no significant past medical history and works as a chef in a local sushi bar. He complains of six to seven watery stools daily with nocturnal symptoms. Diarrhea is associated with abdominal cramps, and he denies any passage of blood. His physical examination, including vital signs, is unremarkable. Laboratory investigation reveals 9.8 g/dL hemoglobin, with a mean corpuscular volume of 110 fL. Peripheral eosinophilia is also noted. A stool sample is sent to the lab and is pending.

Which of the following is the most likely cause of this illness?
A. *Diphyllobothrium latum*
B. *Hymenolepis diminuta*
C. *Hymenolepis nana*
D. *Taenia saginata*
E. *Taenia solium*

Q2. A 52-year-old man with NASH-cirrhosis is admitted to the ICU with red hematemesis and hemodynamic instability. For the past few months, he has been maintained on diuretics but has still required frequent paracenteses for ascites management. An upper endoscopy 44 weeks ago revealed only large esophageal varices that were incompletely eradicated with banding, but the patient did not show up for his scheduled repeat upper endoscopy last week. His initial hemoglobin is 5.8 g/dL. His INR is 1.8, and his platelet count is 94K.

Which of the following treatment options is LEAST likely to benefit this patient?
A. Intravenous proton pump inhibitor drip
B. Intravenous somatostatin analog
C. Endotracheal intubation
D. Intravenous antibiotics
E. Packed red blood cell transfusion

The answers are on page 47.

After POEM, FLIP matches HRM for patient response

BY JIM KLING
MDedge News

Functional lumen imaging probe (FLIP) was equivalent to high-resolution manometry (HRM) in predicting clinical response by Eckardt score 6 months or more after per oral endoscopic myotomy (POEM) for achalasia or esophagogastric junction (EGJ) outlet obstruction (EGJOO).

Measures for clinical response following lower esophageal sphincter myotomy procedures include Eckardt Score, timed barium esophagram, HRM, and FLIP. However, since FLIP is a relatively new technique, there are few clinical data comparing its efficacy versus HRM in patients who have a positive response to POEM measured by the Eckardt score, according to John DeWitt, MD, AGAF, who presented the research at the annual meeting of the American College of Gastroenterology.

FLIP can be performed during a follow-up endoscopy while a patient is sedated, while HRM requires the patient to be awake. Some patients find the procedure intolerable, and Dr. DeWitt estimates that 10%-20% of patients don't return for follow-up assessments because of the discomfort.

"[FLIP] is a relatively new technology, the role of which is still being discovered. We have a lot more information on the diagnosis side of things. The role in follow-up, particularly after myotomy, is really not defined well. This is the first study to my knowledge that has evaluated manometry and FLIP head-to-head to compare patient-reported outcomes," said Dr. DeWitt in an interview. He is a professor of medicine and the director of endoscopic ultrasound at Indiana University Medical Center, in Indianapolis.

Going head-to-head

The researchers conducted a retrospective, single-center study of 265 consecutive patients who underwent POEM for achalasia or EGJOO from 2016 through 2020. A clinical response was defined as an Eckardt score ≤3, EGJ distensibility index (EGJ-DI) higher than 2.8 mm^2/mm Hg, maximum integrated relaxation pressure (IRP) <15 mm Hg, or a maximum EGJ diameter greater than 14 mm at any balloon distension.


Dr. DeWitt

In all, 126 patients returned for follow-up and completed an upper endoscopy with FLIP, HRM, and Eckardt scores within a 6-12 month period after the POEM procedure.

With respect to HRM, an IRP measurement <15 mm Hg predicted post-POEM Eckardt score with a sensitivity of 86.7% (95% confidence interval, 79.3-92.2) and a specificity of 33.3% (95% CI, 4.3-77.7), with an area under the curve of 0.60 (95% CI, 0.39-0.81). A maximum EJG diameter ≥ 14 mm had a sensitivity of 77.5% (95% CI, 69.0-84.6) and a specificity of 33.3% (95% CI, 4.3-77.7), with an AUC of 0.55 (95% CI, 0.34-0.76).

The performance was similar with FLIP: EGJ-DI > 2.8 mm^2/mm Hg at any balloon setting had a sensitivity of 95.0% (95% CI, 89.4-98.1) and a specificity% of 0.0, and an AUC of 0.53 (95% CI, 0.51-0.55). A similar measurement at 40 mL or 50 mL distension had a sensitivity of 93.3% (95% CI, 87.3-97.1) and a specificity of 16.7% (95% CI, 0.4-64.1), with an AUC of 0.55 (95% CI, 0.39-0.72). Receiver operator characteristic analysis showed no significant difference between ability of FLIP and HRM to predict a normal Eckardt score.

If the study is repeated in other patient populations, Dr. DeWitt hopes that it could eliminate manometry altogether in a large majority of patients. "That would be potentially a game changer for bringing patients back to see how well they're doing," said Dr. DeWitt.

Not all patients who undergo POEM would be good candidates for FLIP, said Dr. DeWitt. The study was limited to patients with hypertension in the lower esophageal sphincter. Other disorders such as diffuse esophageal spasm, jackhammer esophagus, and type III achalasia would not likely be candidates for FLIP. "Those patients are going to probably still need manometry because if the esophageal body abnormalities are still present, then repeat testing might need to be performed," said Dr. DeWitt. Still, he estimated about 80% of patients could be eligible for FLIP instead.

Dr. DeWitt had no relevant disclosures.

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Automated duodenoscope cleaner clears out variability

BY JIM KLING
MDedge News

An automated cleaning system outperformed manual cleaning of duodenoscopes in a comparative study. The results included measurements of residual proteins and carbohydrates in all duodenoscope working channels and elevators.

The new automated cleaning system, called the MACH 1, can be added to existing reprocessing areas and is about the size of a commercial washing machine. Cleaning alone takes about 30 minutes, and clean plus high-level disinfection (HLD) takes about an hour, according to Michael O'Donnell, MD, who is a gastroenterology fellow at NYU Langone Health. "Data from prior studies of other automated endoscope reprocessors indicate that MACH 1 more consistently delivers cleaning results that meet or exceed Food and Drug Administration/AAMI (Association for the Advancement of Medical Instrumentation) guidelines," Dr. O'Donnell said in an interview. He presented the study at the annual meeting of the American College of Gastroenterology.

Outbreaks of multidrug resistant organism (MDRO) transmission have been linked to inadequately cleaned duodenoscopes, which has led to greater attention being paid to duodenoscope reprocessing, including prewash, manual cleaning, and disinfection or sterilization, according to Dr. O'Donnell. Postmarketing surveillance by duodenoscope manufacturers Fujifilm, Olympus, and Pentax found a contamination rate of 5.4% for any high-concern organisms – far higher than the initially assumed 0.4%.

The researchers used FDA standard maximum allowed contaminant threshold of < 6.4 mcg/cm^2 protein and < 2.2 mcg/cm^2 carbohydrate. Sampling sites on the duodenoscopes included the elevator wire channel port when present, the biopsy port, the elevator wire channel, the instrument channel, and the elevator recess.

The study included Olympus TJF-Q180V duodenoscopes used in 48 endoscopic retrograde cholangiopancreatography (ERCP) procedures. Each instrument went through standard bedside precleaning; 21 were then cleaned manually by trained technicians following manufacturing instructions, and 27 were cleaned using the automated cleaning system.

In the manually cleaned duodenoscopes, the average level of residual protein was 4.88 mcg/cm^2, versus 0.16 mcg/cm^2 in the automated clean group. The average carbohydrate residues were 1.09 mcg/cm^2 and 0.14 mcg/cm^2, respectively. In all, 2 of the 21 manually cleaned devices had protein levels higher than the FDA threshold, versus none in the automated clean group. In addition, 3 of 21 in the manually cleaned group had higher than threshold carbohydrate levels, versus none in the automated clean group. Overall, 4 of the 27 manually cleaned devices and none of the 21 automated clean devices had protein or carbohydrate levels above FDA thresholds.

Removing variability from cleaning

The cleaning step is critical because failure to remove bioburden can reduce the efficacy of later HLD or sterilization. Cleaning is typically done manually, but the physical complexity of the duodenoscope makes it challenging to do it thoroughly. Manual cleaning is also susceptible to human error or insufficient training, and an observational study found that at least one error occurred in more than 90% of observed cleaning operations (Gastroenterol Nurs. Jul-Aug 2010;33[4]:304-11).


Dr. Young

The MACH 1 uses turbulent flow and resultant shearing forces to clean the duodenoscope. The device is currently used at the medical

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Most stent misdeployments in EUS-GE are manageable

BY HEIDI SPLETE
MDedge News

Most instances of stent misdeployment in cases of endoscopic ultrasound–guided gastroenterostomy (EUS-GE) can be managed endoscopically, based on data from 16 tertiary care centers in the United States and Europe.

EUS-GE provides a viable alternative to traditional surgical gastroenterostomy and stent placement for patients with gastric outlet obstruction (GOO), but the potential for stent misdeployment has limited adoption of the procedure because it remains the most common cause of technical failures and adverse events, Bachir Ghandour, MD, of Johns Hopkins University, Baltimore, and colleagues wrote.

However, data on outcomes and management of stent misdeployment during EUS-GE are limited, and the researchers hypothesized that most stent misdeployments could be managed endoscopically.

In a retrospective study published in Gastrointestinal Endoscopy (2021 Aug 2. doi: 10.1016/j.gie.2021.07.023), the researchers reviewed data from 467 EUS-GE procedures performed for gastric outlet obstruction between March 2015 and December 2020 at eight centers in the United States and eight in Europe. The primary outcome was the rate and severity of stent misdeployment.

Stent misdeployment occurred in 46 patients (9.9%). Of these, 73.2% occurred during the operators' first 13 cases.

The researchers created a classification system of stent misdeployment according to type, depending on which flange was misdeployed.

Type I was the most common, and occurred in 29 patients; this type was defined as "the deployment of the distal flange in the peritoneum and proximal flange in the stomach without evidence of a resulting enterotomy"; type II (14 patients) was defined as "the deployment of the distal flange in the peritoneum and proximal flange in the stomach despite an enterotomy (i.e., visual confirmation of stent having penetrated targeted small bowel, under EUS or fluoroscopy, but migrated out on deployment)"; type III (1 patient) was defined as "the deployment of the distal flange in the small bowel and proximal flange in the peritoneum"; and type IV (2 patients) was defined as "the deployment of the distal flange in the colon and proximal flange in the stomach resulting in a gastrocolic anastomosis," the researchers wrote.

The researchers also classified the stent misdeployment in terms of severity as mild (28 patients), moderate (11 patients), severe (6 cases) or fatal (1 case) based on the American Society for Gastrointestinal Endoscopy lexicon.

Overall, type I was significantly more likely to be mild in severity, compared with type II (75.9% vs. 42.9%; $P = .04$), although the rate of surgical repair was similar between these two types (10.3% vs. 7.1%). Rates of ICU admission were approximately 7% in patients with type I and type II stent misdeployments, and the median postprocedural stay was 4 days for these two groups.

"Stent misdeployment has been commonly reported during EUS-GE and may limit uptake of this more technically challenging procedure."

Same-session salvage management of GOO was achieved by EUS/endoscopic-GE in 24 patients, duodenal stent placement in 6 patients, duodenal dilation in 1 patient, and gastroenterostomy with natural orifice transluminal endoscopic surgery in 3 patients. Of the remaining 12 patients, GOO was managed with subsequent EUS-GE in 6 patients and surgical GI in 6 patients.

The study findings were limited by several factors including the retrospective design and inclusion of a time period that encompassed changes and improvements in the EUS-GE, the researchers noted. The small sample size of type III and IV stent misdeployments prohibited comparison with other types.

However, the cohort size was relatively large, compared with previous studies, and included a range of centers and countries with different strategies for managing stent misdeployments. Given the steep learning curve for EUS-GE, the study findings may help endoscopists better understand the implications and potential consequences of stent misdeployment by classifying the misdeployments into types. "We believe that such a classification or categorization of the different types is important because patient outcomes vary depending on the specific [stent misdeployment] subtype and site of injury. Such a classification will also be very helpful for future research by standardizing the terminology," the researchers said.

"Although [stent misdeployment] is not infrequent during EUS-GE, with a rate of approximately 10%, the majority of cases are mild in severity and can be managed or repaired endoscopically without ill consequences," they concluded. "Surgical intervention is required in less than 11% of the cases."

Data support safe stent use in GI disease

"The lines continue to be blurred between surgical and endoscopic management of gastrointestinal disease, especially with a rise in therapeutic EUS," Gyanprakash A. Ketwaroo, MD, of Baylor College of Medicine, Houston, said in an interview.

"Stent misdeployment has been commonly reported during EUS-GE and may limit uptake of this more technically challenging procedure," Dr. Ketwaroo said. "A comprehensive assessment of stent misdeployment, with suggestions for management and a classification system that predicts outcomes, can help practitioners to more confidently perform this procedure."

Risks associated with misdeployed stents include "inability to perform the endoscopic management of gastric outlet obstruction, as well as adverse events such as peritonitis," said Dr. Ketwaroo. He noted that, in most cases, the defect was closed and same-session salvage was performed, primarily by repeat EUS-GE.

"If the proximal flange is deployed/slips into peritoneum [type III by currently proposed classification system], it can be more difficult to retrieve the stent," but "this complication was treated with surgery, and it was very rare – only one case of this in the study," he explained. "This is a large retrospective multicenter study, which adds validity to the generalizability of the study." However, prospective studies will be needed as EUS-GE is more widely adopted, he added.

The study received no outside funding. Lead author Dr. Ghandour had no financial conflicts to disclose. Other authors disclosed industry relationships, such as consulting for Boston Scientific, Apollo, Olympus America, Medtronic, and GI Supply. Dr. Ketwaroo had no financial conflicts to disclose, but serves as a member of the GI & Hepatology News editorial advisory board.

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device company Parametrik as part of a program that delivers clean duodenoscopes and ultrasound scopes to its customers. The service is currently available only in the New York metro area, but the company intends to expand to other cities in 2022. "This is a huge issue, not only practically for patient care, but it's very much in the public eye. As people who do ERCP, this is a question that patients will come to us with, so we want to be as diligent as possible to drive the bioburden in the scope as low as we can. At least intuitively, that makes sense," said Patrick Young, MD, who comoderated the session and is a professor of medicine at the Uniformed Services University, Bethesda, Md.

He noted that the system has an advantage in that it can be applied to duodenoscopes already in house. Other approaches to the issue of improperly cleaned duodenoscopes include scopes that can be returned to the manufacturer for cleaning, or removable end cap to facilitate access to difficult to clean parts. And then there are disposal duodenoscopes. "If you're throwing a scope away every time you use it, you worry about landfill issues and some of the long term effects of that," said Dr. Young.

Perhaps the most important attribute of the automated cleaning device is that it allows the user to eliminate variation in the cleaning procedure. High-reliability organizations aspire to eliminating variability. "This will probably make it easier to be consistent across technicians – for example, maybe there's one tech that cleans great and one tech that doesn't. This may take some of that out of the equation and give you a more thorough cleaning regardless of circumstance or personnel working on it. So I think it's exciting to have another option that might be less costly than buying new scopes," said Dr. Young.

Dr. O'Donnell and Dr. Young have no relevant financial disclosures.

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Tracking adenomas per colonoscopy shows promise

BY WILL PASS
MDedge News

The number of adenomas per colonoscopy (APC) is inversely correlated with postcolonoscopy colorectal cancer (PCCRC), which supports use of APC as a new quality control measure, according to investigators.

Data from 138 endoscopists showed that patients screened by physicians with higher APCs had significantly lower rates of PCCRC, and an APC of 0.6 offered more protection than either an APC of 0.4 or an adenoma detection rate (ADR) of 25%, reported lead author Joseph C. Anderson, MD, of White River Junction VA Medical Center, Hanover, N.H., and colleagues.

"Unfortunately, APC has never been validated as a quality measure by demonstrating a reduction in PCCRC in exams performed by endoscopists with higher rates," Dr. Anderson said at the annual meeting of the American College of Gastroenterology.

To this end, Dr. Anderson and colleagues reviewed data from the New Hampshire Colonoscopy Registry (NHCR), including 9,023 screening colonoscopies with a follow-up event 6-60 months after the initial exam. Procedures were conducted by 138 endoscopists in New Hampshire, Vermont, Massachusetts, and Maine.

Three quality measures were analyzed for associations with PCCRC: an APC of 0.4, an APC of 0.6, and an ADR of 25%. Hazard ratios were calculated for all PCCRCs, as well as PCCRCs diagnosed at first follow-up event. Rates were reported for two time periods: 6-36 months and 6-60 months.


Dr. Anderson

From 6 to 60 months, 82 cases of PCCRC were diagnosed, among which 50 were diagnosed between 6 and 36 months.

For both periods, all three quality measures were significantly associated with reductions in PCCRC. The higher APC of 0.6, however, offered greater protection, reducing all PCCRCs by 71% and 61% in the shorter and longer period, respectively. In comparison, the lower APC of 0.4 reduced rates by 63% and 53%, while the ADR benchmark reduced rates by 62% and 42%.

These trends were maintained for PCCRCs diagnosed at first follow-up event. An APC of 0.6 was associated with respective reductions of 79% and 65% for the shorter and longer period, compared with 64% and 57% for the lower APC, and 67% and 49% for ADR.

Additional analysis clarified the relationship between APC level and the likelihood of developing PCCRC. In terms of absolute risk, patients screened by an endoscopist with an APC greater than 0.6 had a 0.5% chance of developing PCCRC from 6 to 36 months, compared with 0.7% for an APC of 0.4-0.6, and 2.1% for an APC of less than 0.4 (P = .0001). This pattern held through 60 months, during which time an APC greater than 0.6 was associated with an absolute risk of PCCRC of 0.4%, compared with 0.7% for an APC of 0.4-0.6, and 1.6% for an APC less than 0.4 (P = .0001).

"Our novel data support the use of APC as a quality measure by demonstrating a reduction in PCCRC risk in exams performed by endoscopists with higher APCs," Dr. Anderson concluded, noting that an APC of 0.6 appeared to offer more protection than an APC of 0.4. "I feel that ... APC as a quality measure, now that we've validated it, may be accepted because of its ability to differentiate endoscopists on their adenoma detection skills."


Dr. Hookey

According to Lawrence Hookey, MD, of Queen's University, Kingston, Ont., "It's an important study that will probably contribute to where we're going forward."

Dr. Hookey, chair of the division and medical director of the endoscopy units at Kingston General and Hotel Dieu hospitals, said that APC may overcome the main concern with ADR – that endoscopists who find one adenoma may not be motivated to seek out as many as possible.

"The problem with ADR, in general, is that if you find one polyp, and if ADR is the stat you're living by, then you don't need to find any other polyps, and that obviously doesn't do that patient a favor, necessarily," Dr. Hookey said in an interview. "It does bring them back sooner for surveillance, but it doesn't help remove the rest of the polyps that they have. And not that someone is going to find one polyp and turn off the light and pull the scope out, but you may not be looking as hard."

APC mitigates this issue, he explained, because it determines "whether or not you're truly clearing things out and getting rid of as many [polyps] as possible."

Dr. Hookey said that APC is "probably the best" quality control measure on the horizon, and he suggested that more work is needed to determine the optimal benchmark figure, which should ideally be investigated through larger studies.

"I just want to see it in bigger groups," he said.

The investigators and Dr. Hookey reported no conflicts of interest.

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A single text message links CRC patients to valuable resources

BY NEIL OSTERWEIL
MDedge News

The words "you have colorectal cancer" can concentrate a patient's mind, but certainly not in the way that the clinician delivering the bad news intends.

"A lot of my patients, frankly, have told me that on the first visit the only thing they really hear is the diagnosis of cancer, confirming a malignancy, and everything else that follows is what I call the '2 minutes of terror.' Everything else gets drowned out, and they don't hear my comments on diseases and sometimes my hopefully reassuring comments on prognosis," said Mark A. Lewis, MD, director of the gastrointestinal oncology program at Intermountain Healthcare in Murray, Utah, who is himself a survivor of a rare cancer.

An estimated 150,000 people hear something like "you have colorectal cancer" in the United States each year, according to American Cancer Society estimates.

Even before the diagnosis, the patient, still groggy from sedation after a colonoscopy, may wake up and be told "we've found something; I'll call you in a few days when we get the pathology results."

"This is a great place to get resources here and now. It's a very different shift from going home without anything other than a treatment plan."

You don't have to be a psychiatrist to understand that times of great emotional upheaval, stress, or uncertainty are not ideal for decision-making, especially when the person who is asked to decide is facing a challenge that may seem overwhelmingly complex.

Many patients' first thoughts are to go online for information, but that too can be overwhelming. For example, a Google search for the words "colorectal cancer" turns up roughly 134 million results, in six-tenths of a second, no less.


Dr. Dooreck

There are of course solid, reliable sources for information out there, and reliable information is a very good place to start, as noted by the staff at the Mayo Clinic in Rochester, Minn.

The Mayo website offers 11 tips for coping with a cancer diagnosis. First among the recom-

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Halfpoint Images/Moment/Getty Images

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mendations is "get the facts about your cancer diagnosis," and that's the inspiration behind CRC POP.

Text COLON to 484848

"There are 13,000 of us gastroenterologists in the country, and we diagnose colorectal cancer 150,000 times a year," said CRC POP program creator Brian Dooreck, MD, from Memorial Healthcare System in Pembroke Pines, Fla.

When the doctor tells patients the results "their world is turned upside down, they're shocked, and they don't pick up much after the word 'cancer,' " Dr. Dooreck said in an interview.

Both Dr. Dooreck and Dr. Lewis noted that, after going home with a diagnosis of colorectal cancer, a large majority of patients will go online to find information about their diagnosis.

"We know from studies and anecdotal experience that the odds that someone will try to research their own diagnosis are in the 97% range, and then they're going to run into the pluses and minuses of search engine optimization," Dr. Lewis said.

As even the most casual Internet user can attest, available medical information can range from the practical to the preposterous, from the National Cancer Institute's Cancer.gov to a Facebook post on Aunt Tillie's miracle mayonnaise cure. Helping patients to quickly identify which resources are valuable and trustworthy is the overarching goal of CRC POP, Dr. Dooreck explained.

"What we created with the Colorectal Cancer Provider Outreach Program is that it now allows gastroenterologists to have a conversation with a patient – I can say 'Now listen, take out your phone, and text the world COLON and send it to 484848."

Doing so returns a text in a few seconds with the words "You are not alone. You have our support. Here. Now," and a blue heart emoji, followed by a link that takes the user to a web page with a document containing contact information for the ACS, Colorectal Cancer Alliance, Fight Colorectal Cancer, Colon Cancer Coalition, and Colon Cancer Foundation. Free resources offered by the various organizations include a helpline staffed 24 hours a day (ACS), peer support online or one-to-one and financial assistance (Colorectal Cancer Alliance), access to screening for the under- and uninsured in select areas (Colon Cancer Coalition), and links to a colorectal cancer patient registry (Colon Cancer Foundation).

"I can tell patients 'Hey listen, go home, call these groups, get on their websites. I'll call you in a week; call me if you need me. We're gonna figure this thing out together,' " Dr. Dooreck said. "This is a great place to get resources here and now. It's a very different shift from going home without anything other than a treatment plan."

No gain – except helping patients

After Dr. Dooreck conceived of CRC POP, in September 2020, he described his plan for consolidating links to free resources in a video conference with the organizations he aimed to include. The organizations immediately agreed, and the text-based service, with technology provided free of charge by the marketing company EZ Texting, went live the following month.

"There's no hook, there's no cost, there's no sale, it's not monetized. There's no gain except helping people," Dr. Dooreck emphasized.

Dr. Lewis agreed: "I think it's a great initiative, and it helps unify some of the guidance we give these folks."

Dr. Lewis has the rare perspective of seeing the issue from standpoint of both an oncologist and a patient: Early in his hematology-oncology fellowship at the Mayo Clinic in 2009, he was diagnosed with multiple endocrine neoplasia type 1, and he subsequently underwent surgery to resect pancreatic neuroendocrine tumors.

He says that the buy-in for CRC POP from major support organizations and from gastroenterologists alike is important because most colonoscopies are performed and diagnoses are made in community settings by gastroenterologists who may or may not have formal connections with a cancer center, rather than in large urban or suburban networks affiliated with medical schools.

In most cases, he said, the gastroenterologist makes the CRC diagnosis, and hands the patient off to a surgeon, who may connect with a medical oncologist and/or radiation oncologist depending on the individual patient's circumstance. This process can take weeks, and in the meantime, patients are left in limbo.

Offering patients multiple trustworthy resources through a simple text message is a particularly appealing part of the CRC POP initiative, and can help patients feel that they are more in control of their care, Dr. Lewis said.

Useful resources, multidisciplinary care

The connection to resources offered by CRC POP is valuable and may be especially helpful for community-based or small gastroenterology practices; on the other hand, large academic medical centers may be able to provide more resources on their own.

"We have home-grown support services that we make available to patients if they either ask for them or if we ascertain that those services would be important components of their care," Caroline Kuhlman, a nurse practitioner from the Tucker Gosnell Center for Gastrointestinal Cancers at Massachusetts General Cancer Center in Boston, explained in an interview. "Our approach to a newly diagnosed patient happens in the context of a multidisciplinary visit."

Ms. Kuhlman

"Newly diagnosed patients meet with a surgeon, a medical oncologist, sometimes a radiation oncologist if that's going to be a part their care, and whenever possible during the same outpatient visit. Patients are also provided with written information about colon cancer, and we have a patient resource center that has even more information about support from various organizations," she said.

Patients can also be referred as needed to other resources within the hospital system, including nutritionists, social workers who can help to determine whether patients could benefit from additional social and financial support, and educational resources such as information sessions on what to expect if they receive chemotherapy.

Similarly, Dr. Lewis said that, at Intermountain Health Care, patients newly diagnosed with cancer are contacted within 24 hours by patient navigators who help them manage concerns and expectations about their care and connect them to resources both in the hospital and the community.

Although their own practices differ in size and scope and in the resources they can offer patients, the clinicians interviewed for this article agreed with the central message and purpose of CRC POP: "You are not alone. You have our support."

Dr. Lewis, Dr. Dooreck, and Ms. Kuhlman reported having no conflicts of interest relevant to the subjects discussed in this article.

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Linked-color imaging outperforms other modalities

BY HEIDI SPLETE
MDedge News

Linked-color imaging (LCI) significantly increases the detection of adenomas in screening colonoscopies compared to white-light imaging (WLI) and blue-laser imaging (BLI)–bright, according to data from 205 adults who underwent screening colonoscopies.

LCI is a relatively new image-enhancement method designed to better identify adenomatous lesions by increasing the contrast of the mucosal surface, wrote Carlos E.O. dos Santos, MD, of Pontifícia Universidade Católica do Rio Grande do Sul in Porto Alegre, Brazil, and colleagues. Their report is in the Journal of Clinical Gastroenterology (2021 Aug. doi: 10.1097/MCG.0000000000001601). With LCI, the lesions are more vascularized, and thus become reddish due to color contrast of hemoglobin present in capillary vessels, whereas the surrounding mucosa becomes whitish. Until this new study, the potential of LCI to detect adenomas compared with other imaging had not been evaluated.

The researchers randomized 205 patients with a total of 296 colorectal lesions to WLI, BLI-bright, or LCI; 70 patients were examined by WLI, 66 by BLI-bright, and 69 by LCI. The average age of the patients was 59 years, and 52% were women. The primary outcome measures were adenoma detection rate (ADR), mean number of adenomas per patient, and withdrawal time.


Dr. Gellad

A total of 251 adenomas were detected, with an overall ADR of 62%. The total number of adenomas detected by each method was 112 by LCI, 71 by WLI, and 68 by BLI-bright.

The ADR was significantly higher for patients in the LCI group compared with those in the WLI group (71% vs. 52.9%, $P = .04$). ADR for LCI was greater than the ADR for BLI-bright, but the difference was not significant (71% vs. 62.1%, $P = .28$). No significant differences in ADR were noted between the WLI and BLI-bright groups.

The mean number of adenomas identified per patient was 1.17 overall, but significantly higher in the LCI group compared to the WLI and BLI-bright groups (1.62, 1.01, and 1.03, respectively, $P = .02$). Mean withdrawal times were not significantly different among the three groups and ranged from approximately 10 to 11 minutes. An analysis of secondary outcomes showed no differences among the groups in terms of size and morphology of the adenomas, or in the detection of sessile serrated adenomas or polyps.

The researchers noted that the study findings were limited by several factors including the use of data from a single center with a high level of experience in image-enhanced endoscopy and by the relatively small sample size.

Nevertheless, concluded the researchers, "It is evident that better visibility of the mucosa is a key factor for the detection of neoplastic lesions," and the results support the potential of LCI given the demonstrated superiority of LCI over WLI

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AI could prevent missed polyps, interval cancer

Colonoscopy *from page 1*

those appearing partly or fully in the visual field but missed by an endoscopist, wrote Jeremy R. Glissen Brown, MD, of Harvard Medical School, Boston, and colleagues. While retrospective and prospective studies in China, Italy, and Japan have shown that deep-learning CADe improves adenoma identification during colonoscopy, there have been no prospective U.S. studies on CADe in a diverse population, they noted.

In the study published in Clinical Gastroenterology and Hepatology (2021 Sep. doi: 10.1016/j.cgh.2021.09.009), the researchers reviewed data from 223 adults aged 22 years and older who underwent screening colonoscopies across four U.S. academic medical centers between 2019 and 2020. The procedure indication was primary colorectal cancer screening for 59.6% of the patients and postpolypectomy surveillance for 40.4%. Participants were randomized to receive either CADe colonoscopy first or HDWL colonoscopy first; the patients immediately underwent the other procedure in tandem fashion from the same endoscopist.

The primary outcome of the study was adenoma miss rate (AMR), defined as "the number of histologically confirmed adenomas detected during the second colonoscopy in either arm divided by the total number of adenomas detected during both procedures." Sessile serrated lesion (SSL) miss rates and adenomas per colonoscopy (APC) were secondary outcomes.

Overall, the primary outcome of AMR was significantly lower in the CADe-first group, compared with the HDWL-first group (20.12% vs. 31.25%; *P* = .0247), with an odds ratio of 1.8048 (95% CI, 1.0780-3.0217). The CADe-first group yielded a lower SSL miss rate, compared with the HDLW-first group (7.14% vs. 42.11%; *P* = .0482), as well as a lower polyp miss rate (20.70% vs. 33.71%; *P* = .0007). The first-pass number of APC was significantly higher in the CADe-first group, compared with the HDWL-first group (1.19 [SD 2.03] vs. 0.90 [SD 1.55]; *P* = .0323). In addition, the first-pass adenoma detection rate (ADR) was not significantly different in the CADe-first group, compared with the HDWL-first group (50.44% vs. 43.64%; *P* = .3091), and the median withdrawal time was significantly shorter with CADe, compared with HDWL (9.5 minutes vs. 8.5 minutes; *P* = .0098).

There were no significant observable differences between the two groups regarding missed adenomas arranged by size or location. Moreover, there were no significant differences in miss rates for hyperplastic polyps or advanced adenomas. Factors significantly associated with missed adenomas included being in the HDLW-first group, age 65 years or younger, and the right colon vs. other locations. No immediate adverse events occurred in either group.

According to the researchers, while previous studies in China and Italy have shown increased ADR using CADe systems, these results are not generalizable to the U.S. population for several reasons, notably the studies' inclusion of colonoscopy indications other than colorectal cancer screening and surveillance. Though the present study showed a significantly lower AMR with CADe, it still represents missed adenomas. The researchers note: "In the present study, in which CADe detected 285 polyps, there were only three false negatives (defined as polyps that were visualized by the endoscopist but not by the CADe system). Overall, this suggests that the 'missed polyps' in the CADe arm may have been obscured behind folds rather than in the visual field." They added, "Further research is needed on combining CADe technologies with mucosal exposure devices, as the benefits of these tools for polyp detection may be additive."

The study findings were limited by several factors, including the inability to detect a difference in overall ADR, the limited generalizability of the tandem study design to real-world practice, the inclusion of only experienced endoscopists, and the use of a second monitor that may have impacted gaze patterns, the researchers noted. However, the results represent the first examination of deep-learning CADe in a diverse U.S. population and showed a decrease in adenoma miss rates and decreased miss rates for polyps and SSLs, compared with HDWL. Based on these findings, the authors concluded CADe "has the potential to decrease interprovider variability in colonoscopy quality by reducing adenoma miss rate even in experienced providers."

Reducing miss rates matters

"Missed adenomas can be associated with the development of interval colorectal cancer, so whether novel technologies such as artificial intelligence-based computer-aided polyp detection system can decrease adenoma miss rate is of interest," said Atsushi Sakuraba, MD, of the University of Chicago, in an interview.

Dr. Sakuraba said he was not surprised by the current study findings, as several pilot and randomized studies have shown the benefits of AI-based polyp detection systems. As for how the AI-assisted technology might improve practice, he said it may be a valuable addition. "Adenoma miss rate was significantly lower with an AI-based polyp detection system, so it might lead to decreased colorectal cancer," he explained. "Various methods to improve adenoma detection should complement each other."

Dr. Sakuraba also commented that additional research is needed outside of academic centers, noting "further studies in the community setting involving various endoscopists are required to confirm generalizability."

Lead author Dr. Glissen Brown had no financial conflicts to disclose. This was an investigator-initiated study, with research software and study funding provided by Wision. Dr. Sakuraba disclosed collaborative research with Fujifilm, which was not involved in this study.

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Continued from previous page

for colorectal adenoma detection and the mean number of adenomas detected per patient.

The researchers said that further single and multicenter randomized studies are needed to validate the results and to confirm whether one image-enhancement system is superior to the other for increasing the ADR.

Door is open for better detection tools

In an interview, Atsushi Sakuraba, MD, of the University of Chicago, who was not involved with the study, said, "Linked-color imaging provides an increased contrast of the mucosal surface and enhances the findings of adenomatous lesions in comparison to white-light endoscopy and has been shown to be effective in detecting adenomas, so the findings of the present study are not surprising."

LCI provides clearer and brighter images by enhancing the differences in color contrast, and therefore does not cause the impaired visibility that can occur with narrow band imaging or BLI images, Dr. Sakuraba said. However, he noted, not all endoscopy centers carry the scopes equipped with LCI, which is a barrier to widespread use. Dr. Sakuraba said that multicenter studies need to be undertaken to confirm the generalizability of the results of the present study.

"There is now convincing evidence that increasing adenoma detection rate is associated with fewer missed cancers and lower mortality from colorectal cancer," said Ziad F. Gellad, MD, AGAF, of Duke University, Durham, N.C., who was also not involved with the study. "Understanding the relative benefits and drawbacks of available tools and technologies in the market can help practicing gastroenterologists decide where to invest their time and resources to improve care."

Dr. Gellad said he was not surprised by the enhanced detection using LCI, as the study is not the first to evaluate this technology. "However, I was surprised by how high the ADR was in the screening population (62%)," said Dr. Gellad, observing that this exceeds benchmarks set by the society. "We don't have a full understanding of the demographic characteristics of this screening population. ... Nonetheless, I think this paper adds to accumulating data that current benchmarks may be too low."

Dr. Gellad said the findings of the study would not change practice, but the results are a "valuable contribution to the literature and will empower future larger studies as well as meta-analyses." He called for larger studies in nonspecialized centers to relate the findings from this small study to general practice.

The study received no outside funding. The researchers had no financial conflicts to disclose. Dr. Sakuraba disclosed collaborative research relationships with Fujifilm, the manufacturer of the imaging equipment used in the study. Dr. Gellad had no financial conflicts to disclose but serves on the editorial board of GI & Hepatology News.

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Dupilumab shows long-term efficacy in EoE

BY JIM KLING
MDedge News

Data from the 28-week extension of the Liberty EoE TREET phase 3 clinical trial showed that the anti–interleukin-4/IL-13 antibody dupilumab led to long-term improvement in eosinophil count, histology, and patient-reported symptoms of eosinophilic esophagitis (EoE) out to 28 weeks. Dupilumab is Food and Drug Administration approved for the treatment of atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.

Many patients don't respond to the standard therapies of proton pump inhibitors, steroids, or diet. Some evidence suggests that EoE might be driven by type 2 inflammation, and dupilumab's effect on the shared receptor of IL-4 and IL-13 directly counters that pathway.

"The bottom line is that people who responded up front to dupilumab maintain that response to a year, and the people on placebo gained a similar response as the people who were treated. It looked good. It was histologic, symptomatic, and endoscopic outcomes," said Evan Dellon, MD, AGAF, professor of medicine and epidemiology at the University of North Carolina at Chapel Hill, in an interview. Dr. Dellon presented the research at the annual meeting of the American College of Gastroenterology.

Many of the patients in the new study were steroid refractory, making it a difficult population to treat, according to Dr. Dellon. "You can't compare to the steroid-treated patients, but the 6-month data showed about a 60% response rate histologically, which is right up there with where steroids and diet are for easier-to-treat patients. So the fact that it's a harder-to-treat cohort is pretty impressive from that standpoint," said Dr. Dellon.

At ACG 2021, Dr. Dellon reported on 52-week results, where all patients from both treated and placebo groups received dupilumab after the initial 24-week phase. Dupilumab reduced dysphagia symptoms as measured by the absolute change in DSQ score at 24 weeks (–21.9 vs. –9.6; $P < .001$). At 52 weeks, the dupilumab group showed a change of –23.4 from the start of the study, and the placebo-to-dupilumab group had a DSQ score change of –21.7. Dupilumab also led to a greater percentage reduction in DSQ score by 24 weeks (69.2% versus 31.7%; $P < .001$); at 52 weeks, the dupilumab group had a 75.9% reduction and the placebo-to-dupilumab group had a 65.9% reduction (no significant difference).

The dupilumab group had a greater proportion of patients who achieved peak esophageal eosinophil count of 6 eosinophils or less per high power field at 24 weeks (59.5% vs. 5.1%); at 52 weeks, 55.9% had achieved this measure, versus 60.0% of the placebo-to-dupilumab group. At 24 weeks, the dupilumab group had a 71.2% reduction in peak eosinophil count from baseline versus –3.0% in placebo ($P < .001$). At week 52, the reductions were 88.6% and 83.8%, respectively.

"People who responded up front to dupilumab maintain that response to a year," said Dr. Evan Dellon.

Histology features were improved with dupilumab. At week 24, the absolute change in histology scoring system mean grade score (histologic severity) from initial baseline was greater in the dupilumab group (least squares mean, –0.761 vs. –0.001; $P < .001$). The improvement continued at week 52 (LS mean, –0.87) and occurred in the placebo-to-dupilumab group (LS mean, –0.87). The dupilumab group had a greater absolute change in mean stage score at 24 weeks (histologic extent, LS mean, –0.753 vs. –0.012; $P < .001$) and 52 weeks (LS mean, –0.89), while the placebo-to-dupilumab group achieved a similar change at 52 weeks (LS mean, –0.87).

Endoscopic features improved in the dupilumab group as measured by endoscopic reference score at 24 weeks (LS mean, –3.2 versus –0.3; $P <.001$) and at 52 weeks (LS mean, –4.1). The placebo-to-dupilumab group had a similar outcome at 52 weeks (LS mean, –3.9).

Dupilumab was well tolerated, with the only significant difference in treatment-emergent adverse events being injection-site reactions and injection-site erythema.

"I thought the data was really impressive and compelling," said Amy Oxentenko, MD, AGAF, chair of medicine at the Mayo Clinic in Phoenix, who comoderated the session. "It'd be nice to have something like this that is a targeted therapy that clearly shows improvement in not only some of the symptoms and histology, but also having an impact possibly on that fibrotic piece, which I think is really the area of morbidity in these patients long term."

If approved, dupilumab could improve compliance among patients, who sometimes struggle with taking topical steroids properly, said comoderator David Hass, MD, who is an associate clinical professor at Yale University, New Haven, Conn. He also agreed that the potential for remodeling would be a significant benefit over steroids.

One concern with dupilumab would be any potential for immune suppression. "It's always something to think about," Dr. Hass said.

LIBERTY EoE TREET was funded by Sanofi and Regeneron. Dr. Dellon has consulted and received research support from numerous pharmaceutical companies. Dr. Oxentenko and Dr. Hass have no relevant financial disclosures.

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Stool tests for *H. pylori* resistance match gastric biopsies

BY WILL PASS
MDedge News

Using stool samples to test for *Helicobacter pylori* antibiotic resistance provides highly similar results to those of gastric biopsy samples, which suggests that stool testing may be a safer, more convenient, and more cost-effective option, according to investigators.

Head-to-head testing for resistance-associated mutations using next-generation sequencing (NGS) showed 92% concordance between the two sample types, with 100% technical success among polymerase chain reaction (PCR)–positive stool samples, lead author Steven Moss, MD, AGAF, of Brown University, Providence, R.I., and colleagues reported.

"*H. pylori* eradication rates have declined largely due to rising antimicrobial resistance worldwide," Dr. Moss said at the annual meeting of the American College of Gastroenterology. "There is therefore a need for rapid, accurate, reliable antibiotic resistance testing."

According to Dr. Moss, molecular resistance testing of gastric biopsies yields similar results to culture-based testing of gastric biopsies, but endoscopic sample collection remains inconvenient and relatively costly, so "it is not commonly performed in many GI practices.

"Whether reliable resistance testing by NGS is possible from stool samples remains unclear," Dr. Moss said.

To explore this possibility, Dr. Moss and colleagues recruited 262 patients scheduled for upper endoscopy at four sites in the United States. From each patient, two gastric biopsies were taken, and within 2 weeks of the procedure, prior to starting anti–*H. pylori* therapy, one stool sample was collected.

For gastric biopsy samples, *H. pylori* positivity was confirmed by PCR, whereas positivity in stool samples was confirmed by both fecal antigen testing and PCR. After confirmation, NGS was conducted, with screening for resistance-associated mutations to six commonly used antibiotics: clarithromycin, levofloxacin, metronidazole, tetracycline, amoxicillin, and rifabutin.

Out of 262 patients, 73 tested positive for *H. pylori* via stool testing; however, 2 of these patients had inadequate gastric DNA for analysis, leaving 71 patients in the evaluable dataset. Within this group, samples from 50 patients (70.4%) had at least one resistance-association mutation.

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Vonoprazan beats PPIs in *H. pylori* eradication

BY JIM KLING
MDedge News

In the treatment of *Helicobacter pylori* infection, combination therapies using the oral potassium-competitive acid blocker vonoprazan were superior to standard proton pump inhibitor (PPI)–based triple therapy, producing higher eradication rates, according to combined data from a U.S. and a European phase 3 randomized, controlled trial.

Vonoprazan has been submitted to the Food and Drug Administration for approval with a Fast Track designation in combination with amoxicillin and clarithromycin (triple therapy) or amoxicillin alone (dual therapy) for treating *H. pylori* infection. It has already been approved in Japan for the treatment of gastric and duodenal ulcers, reflux esophagitis, secondary prevention of low-dose aspirin– or nonsteroidal anti-inflammatory drug–induced gastric mucosal damage, and for first and second-line *H. pylori* eradication therapy.

The results were presented by William Chey, MD, AGAF, at the annual meeting of the American College of Gastroenterology. Dr. Chey is a professor of medicine and director of the GI physiology laboratory at Michigan Medicine.

Study details

The study included 1,046 treatment-naive patients who had dyspepsia, a recent or new diagnosis of a nonbleeding peptic ulcer, a history of a peptic ulcer, or long-term stable use of an NSAID. Patients were randomized to PPI-based triple therapy (lansoprazole, amoxicillin, clarithromycin), vonoprazan triple therapy (plus amoxicillin, clarithromycin), or vonoprazan dual therapy (amoxicillin). The treatment period was 14 days, followed by 13C urea breath test (UBT) 4 weeks after treatment.

Among patients with *H. pylori* strains that were not resistant to clarithromycin, the PPI-based triple-therapy group had an eradication rate of 78.8%, compared with 84.7% in the vonoprazan triple-therapy group ($P < .0001$) and 78.5% in the vonoprazan dual-therapy group ($P = .0037$). In the per protocol analysis, PPI-based triple therapy eradicated *H. pylori* 82.1% of the time, compared with 90.4% in the vonoprazan triple-therapy group ($P < .0001$) and 81.2% in the vonoprazan dual-therapy group ($P = .0077$). Both vonoprazan treatment groups were noninferior to PPI-based triple therapy.


Jim Kling/MDedge News

Vonoprazan is more stable in acid than are PPIs, and produces greater and more durable acid reduction, said Dr. William Chey.

A prespecified exploratory analysis found that vonoprazan triple therapy outperformed PPI-based triple therapy in the modified intention-to-treat population ($P = .0408$) and the per protocol population ($P = .0059$).

Among patients with clarithromycin-resistant strains of *H. pylori*, in the modified intention-to-treat population, 31.9% achieved eradication with PPI triple therapy, compared with 65.8% gin the vonoprazan triple-therapy group, and 69.6% in the vonoprazan dual-therapy group. In the per protocol population, the numbers were 29.0% versus 67.2% and 79.5%, respectively ($P < .0001$ for both versus PPI triple therapy).

Among all patients, in the modified intention-to-treat population, 68.5% achieved eradication with PPI triple therapy, 80.8% with vonoprazan triple therapy ($P = .0001$), and 77.2% with vonoprazan dual therapy ($P = .0063$). In the per protocol population, the numbers were 70.0%, 85.7% ($P < .0001$), and 81.1% ($P = .0013$), respectively.

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Among all 71 individuals, 65 patients (91.5%) had fully concordant results between the two sample types. In four out of the six discordant cases, there was only one difference in antibiotic-associated mutations. Concordance ranged from 89% for metronidazole mutations to 100% for tetracycline, amoxicillin, and rifabutin mutations.

"It is now possible to rapidly obtain susceptibility data without endoscopy," Dr. Moss concluded. "Using NGS to determine *H. pylori* antibiotic resistance using stool obviates the cost, inconvenience, and risks of endoscopy resistance profiling."

Dr. Moss noted that the cost of the stool-based test, through study sponsor American Molecular Laboratories, is about $450, and that the company is "working with various insurance companies to try to get [the test] reimbursed."

For any cases of *H. pylori* infection that do not have resistance testing results, Dr. Moss recommended first-line treatment with quadruple bismuth–based therapy; however, he noted that "most gastroenterologists, in all kinds of practice, are not measuring their eradication success rate ... so it's really difficult to know if your best guess is really the appropriate treatment."

According to Lukasz Kwapisz, MD, of Baylor College of Medicine, Houston, the concordance results are "encouraging," and suggest that stool-based testing "could be much easier for the patient and the clinician" to find ways to eradicate *H. pylori* infection.

Dr. Kwapisz predicted that it will take additional successful studies, as well as real-world data, to convert clinicians to the new approach. He suggested that the transition may be gradual, like the adoption of fecal calprotectin testing.

"I don't know if it's one singular defining study that will tell you: 'Okay, we all have to use this [stool-based resistance testing],' " he said. "It kind of happens over time – over a 2- or 3-year stretch, I would think, with positive results."

The study was supported by American Molecular Labs. The investigators disclosed additional relationships with Takeda, Phathom, and Redhill. Dr. Kwapisz reported no conflicts of interest.

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Safety outcomes were similar among the three groups, with treatment-emergent adverse events occurring in 34.5% of the PPI triple-therapy group (1.2% discontinued), 34.1% of the vonoprazan triple-therapy group (2.3% discontinued), and 29.9% in the vonoprazan dual-therapy group (0.9% discontinued).

Fighting resistance

The efficacy of PPI-based clarithromycin-based triple therapy has fallen below 80% in the United States and Europe over the past few decades, largely because of antibiotic resistance, said Dr. Chey.

Vonoprazan is more stable in acid than are PPIs, and produces greater and more durable acid reduction, according to Dr. Chey. That's important for two reasons: One is that some antibiotics are acid labile, and so may have their efficacy directly impacted in a more acidic environment. The other factor is that most antibiotics work better on bacteria that are actively replicating, and *H. pylori* reproduces better in a more neutral environment. "So, you increase the replication, you increase the bioavailability of the antibiotics. And therefore, hopefully, that underlies why we see it working better in the patients with [antibiotic] resistance," Dr. Chey said in an interview.

It remains to be seen whether or not the drug will receive FDA approval, but he pointed to other regimens like bismuth quadruple therapy and rifabutin-based triple therapy that are already available. "If I had the choice, I would never use a PPI-based triple therapy again. People should not be doing that," said Dr. Chey.

"More successful *H. pylori* eradication regimens are certainly needed, and these results are particularly relevant and interesting given the increasing failure of initial treatment regimens," said Kimberly Harer, MD, who moderated the session. She noted that the secondary analysis of patients with clarithromycin-resistant infections was particularly relevant. "The superiority analysis indicating vonoprazan triple therapy resulted in increased *H. pylori* eradication compared to lanzoprazole triple therapy was especially interesting," said Dr. Harer, who is a clinical lecturer at University of Michigan Health, Ann Arbor.

One downside to the study is that it didn't compare vonoprazan combinations to quadruple therapy of a PPI, bismuth, tetracycline, and a nitroimidazole, said Joseph Jennings, MD, who was asked to comment on the study. Other treatment approaches include sequential antibiotics and other combinations. Dr. Jennings also highlighted the findings that the vonoprazan regimens were superior against clarithromycin-resistant strains. "The more different regimens we can add to the armamentarium, the better chance we have because the resistant patterns fluctuate all throughout the world," said Dr. Jennings, who is an assistant professor of medicine at Georgetown University and director of the center for GI bleeding at MedStar Georgetown University Hospital, both in Washington.

He also pointed out that physicians can face a conundrum when patients fail multiple lines of therapy and have testing done that shows high levels of resistance. Some have allergies that prevent them from turning to other antibiotics. "That's a market where lots of doctors struggle. Something like this would be a nice add-on," said Dr. Jennings.

The study was funded by Phathom Pharmaceuticals. Dr. Chey has consulted and/or received research support from various companies including Phathom Pharmaceuticals. Dr. Harer and Dr. Jennings have no relevant financial disclosures.

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Humoral immune response detected in most IBD patients after mRNA COVID vaccination

BY WILL PASS
MDedge News

Most patients with inflammatory bowel disease (IBD) develop a humoral immune response after completing an mRNA SARS-CoV-2 vaccine series, according to data from almost 800 patients.

Anti–receptor binding domain IgG antibodies specific to SARS-CoV-2 were detectable in 95% of patients, with "generally similar" results across vaccine type, age group, and medication class, apart from corticosteroid users, who had an 86% antibody detection rate, reported lead author Kimberly N. Weaver, MD, of the University of North Carolina at Chapel Hill, and colleagues.

"Patients with IBD on immunosuppressive medications have the potential for attenuated response to the SARS-CoV-2 vaccination," Dr. Weaver said at the annual meeting of the American College of Gastroenterology.

To better characterize antibody responses after receiving an mRNA vaccination series, Dr. Weaver and colleagues launched the PREVENT-COVID trial, including the present dataset of 787 patients with IBD older than 12 years, all of whom provided serum samples 8 weeks after completing an mRNA vaccine series. Patients with positive nucleocapsid antibody (indicating prior infection), and/or those who reported prior COVID-19 infection, were excluded. Most patients were White (95%) and female (73%), with an average age of 48 years.

At 8 weeks, 752 out of 787 patients had detectable antibodies (95%). Antibody rates were highest among patients receiving vedolizumab monotherapy (n = 83; 99%) or ustekinumab monotherapy (n = 102; 99%), followed by mercaptopurine, azathioprine, or methotrexate monotherapy (n = 67; 97%); anti–tumor necrosis factor monotherapy (n = 270; 96%); mesalamine, sulfasalazine, or budesonide monotherapy or no medication (n = 143; 95%); and finally anti-TNF/immunosuppressive combination therapy (n = 75; 86%). Median and mean antibody titers were lowest for anti-TNF combination therapy and highest for vedolizumab.

Thirty-five patients taking corticosteroids had an antibody detection rate of 85.7% (95% CI, 70.6-93.7), compared with 95.9% (95% CI, 94.2-97.1) among nonsteroid users. In contrast, antibody detection rates were not significantly affected by age or vaccine type.

"Reassuringly, most IBD medications do not prevent an initial antibody response after SARS-CoV-2 vaccination, and this is unlike other classes of immune suppression such as B-cell depletion therapy," Dr. Weaver concluded. "Additional data are forthcoming on a larger subset of participants in the PREVENT-COVID study which will allow for analysis of factors associated with humoral immune response and potential optimization of immunization strategies." She described a dataset of about 500 IBD patients in which booster vaccines overcame poor antibody responses to the initial vaccine series.

'The data we need'

Serre-yu Wong, MD, PhD, of Icahn School of Medicine at Mount Sinai, New York, agreed that the findings should offer some reassurance.


Dr. Wong

"At the end of the day we have really nice seroconversion rates for the IBD population," Dr. Wong said.

In April 2021, Dr. Wong and the ICARUS-IBD Working Group published a similar report (Gastroenterology. 2021 Aug;161[2]:715-8.e4) of 48 patients with IBD receiving biologic therapies, among whom the seroconversion rate was 100%.

"A lot of the early data, including ours, are on infusion medications, and that's sort of a practical thing because those were the only patients we could get samples from, but [Dr. Weaver and colleagues] were able to get samples from patients not on medications, on oral medications, and on other injection medications that people can take at home, and these are really the data we need for all of our other IBD patients," Dr. Wong said.

Dr. Wong highlighted that both trials showed some IBD patients generating "very, very high" titers, many of them above the threshold needed for donating convalescent plasma for COVID-19 treatment; still, exact titer levels needed to protect against SARS-CoV-2 infection remain unclear.

Although postvaccination antibody testing is not recommended by the Centers for Disease Control and Prevention, Dr. Wong said that many patients check their titers anyway, leading to anxiety if antibodies are low or undetectable.

"I know that it's very disconcerting sometimes when you don't see an antibody response, and this is one of the hardest things to try to explain to patients," Dr. Wong said. "[It's necessary] to have a frank discussion about the fact that we don't know the magic level of antibodies, and that there are also other parts of the immune system that we haven't tested with antibodies. We haven't tested the T-cell response, and we do know you can have a T-cell response even if you don't have a B-cell response."

Dr. Wong suggested that more work is needed to determine the impact of the IBD disease process on susceptibility to SARS-CoV-2 infection, and the rates of antibody responses for the various other vaccines being used around the world.

The PREVENT-COVID study was supported by the Leona M. and Harry B. Helmsley Charitable Trust. The investigators disclosed additional relationships with AbbVie, Johnson & Johnson, Genentech, and others. Dr. Wong reported no relevant conflicts of interest.

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No decline in stomas despite increasing anti-TNF use for Crohn's

BY JIM KLING
MDedge News

Despite increasing use of anti–tumor necrosis factor (TNF) medications in recent years and a lower rate of proctectomy, there has been no decline in stoma incidence among Crohn's disease (CD) patients, according to a new retrospective analysis of a Swedish population database.

The overall 5-year stoma incidence was 2.5%, and there was no significant difference between calendar periods, wrote Åsa H. Everhov, MD, PhD, of the Karolinska Institutet, Stockholm, and colleagues. Their report is in Inflammatory Bowel Diseases (2021 Oct. doi: 10.1093/ibd/izab245). Previous population studies looking at temporal trends have found mixed results with respect to stoma formation. However, many previous studies analyzed cohorts from referral centers that included patients with more severe disease. Others had small sample sizes.

"This is somewhat surprising as the rate of overall surgery for Crohn's has decreased with the advent of biologic therapies," said Miguel Regueiro, MD, AGAF, who was asked to comment on the study. He is chair of the Digestive Disease and Surgery Institute, and professor of medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

Dr. Regueiro pointed out that the rate of stoma creation was quite low, and characteristics of the disease may explain the lack of a trend. For example, anorectal disease, especially when accompanied by fistula and strictures, is often medication refractory. "Although the study could not delineate this, it is my clinical practice experience that some patients present with destructive anorectal disease early, and that despite medications the 'damage is too far gone' to reverse," said Dr. Regueiro.

The findings shouldn't affect patient management or counseling, according to Stephen Hanauer, MD, AGAF, professor of medicine at Northwestern University, Chicago, who was not involved in the study. "The indications for surgery in Crohn's disease have not changed with the advent of newer therapies. Complications such as strictures and abscesses are still treated with similar surgeries."

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The study authors noted that the findings are consistent with previous studies suggesting that the rate of abdominal surgery had begun to decline before anti-TNF drugs were introduced. The Swedish National Patient Register used in the current work includes only inpatient data before 2001, preventing a broader analysis prior to 1999, when infliximab gained approval in Sweden. But the researchers looked at time from first surgery to stoma, and found a decline in stoma formation between 1994 and 1997. A similar analysis found no decrease in the 2000s.

The researchers pointed out that anti-TNF inhibitor use would be expected to reduce the rate of stomas by inducing remission, although temporary stomas may be created to relieve symptoms while waiting for the medication to take effect. But anti-TNF agents could also encourage patients and physicians to postpone surgery. The delay could raise the chance of surgical complications, which in turn could lead to creation of a temporary stoma. Permanent stomas are typically created in cases of severe perianal CD.

The study could come as a disappointment to some patients and physicians, according to the authors. "The more active and early use of anti-TNF [therapeutics], in combination with the decreasing incidence of abdominal surgery in general for CD, has raised hopes of decreased incidence of stoma formation, but this was not observed in the present study," the authors wrote.

But the news wasn't all bad. The study found a lower cumulative stoma incidence than had previous studies, and the incidence of permanent stoma was just 0.8% at 5 years, "which should be reassuring for patients," according to the authors.

CD patients often fear that a stoma will become necessary, but a stoma can be quite beneficial, allowing patients to regain some control over their lives. Qualitative studies showed that both patients and clinicians described outcomes of stoma placement as exceeding expectations. The authors encouraged clinicians to discuss the possibility of a stoma early on in the treatment process and to avoid referring to it as a "last resort."

The new study analyzed data between 2003 and 2014, from 18,815 Crohn's disease patients who had not undergone previous surgery. The median age was 39 years, 53% were women, and 12% were pediatric patients.

After a median follow-up of 9.6 years, 9.5% of patients had perianal disease. Overall, 36% of patients had been treated with immunomodulators, and 17% with anti-TNF agents; 3.5% had stoma surgery, and just 0.05% underwent proctectomy.

Among those who had a stoma placed, the median age at diagnosis was 47 years, and 53% were men. In all, 12.6% had perianal disease at diagnosis, and 24.5% had perianal disease by the end of follow-up; 43% had received immunomodulators, and 26% anti-TNF agents. Among stomas, 64% were ileostomies, and 44% were temporary, with 88% of removals performed within 2 years of surgery.

The calendar periods of CD onset (2003-2006, 2007-2010, and 2011-2014) had similar rates of cumulative stoma placement (log rank test, $P = .61$). Overall, the 1-year cumulative incidence of stoma was 1.3%, the 3-year incidence was 1.9%, and the 5-year incidence was 2.5%.

The cumulative incidence of ever-use of anti-TNF agents increased with each successive calendar period ($P < .001$), but there was no significant difference in cumulative stoma incidence ($P = .07$).

One limitation of the study is the lack of detailed patient characteristics, and another is the short follow-up for patients diagnosed during 2011-2014. Another is that the results may not be generalizable to a U.S. population.

The study authors have received funding and consulted for various pharmaceutical companies. Dr. Regueiro has received grants from and has consulted or been on a scientific advisory board for AbbVie, UCB, and Janssen. Dr. Hanauer has no relevant financial disclosures.

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A pill for *C. diff* increases microbiome diversity

BY LAIRD HARRISON

An oral treatment with freeze-dried human stool can successfully treat *Clostridioides difficile* infections by increasing the diversity of microorganisms in the colon, researchers say.

CP101, under development by Finch Therapeutics, proved more effective than a placebo in preventing recurrent infections for up to 24 weeks. The CP101 capsules contain a powder of freeze-dried human stools from screened donors. They restore natural diversity that has been disrupted by antibiotics, said Jessica Allegretti, MD, MPH, a gastroenterologist at Brigham and Women's Hospital in Boston.

The treatment offers an alternative to fecal microbiota transplant, which can effectively treat antibiotic-resistant *C. difficile* infections but is difficult to standardize and administer – and doesn't have full approval from the U.S. Food and Drug Administration, she added.

Dr. Allegretti is an author on three presentations of results from PRISM3, a phase 2 trial of CP101. They were presented at the annual meeting of the American College of Gastroenterology.

The study enrolled 198 people who received antibiotics for recurrent *C. difficile* infections. Some patients had two or more recurrences, while others had only one recurrence but were 65 years of age or older.

"That was a unique aspect of this study, to see the effect of bringing a therapy like CP101 earlier in the treatment paradigm," said Dr. Allegretti. "You can imagine for an older, frail, or more fragile patient that you would want to get rid of this [infection] earlier."

After waiting 2-6 days for the antibiotics to wash out, the researchers randomly assigned 102 of these patients to take the CP101 pills orally and 96 to take placebo pills, both without bowel preparation.

The two groups were not significantly different in age, gender, comorbidities, the number of *C. difficile* recurrences, or the type of test used to diagnose the infection (PCR-based vs. toxin EIA-based).

After 8 weeks, 74.5% of those given the CP101 pills had not had a recurrence, compared with 61.5% of those given the placebo. The difference was just barely statistically significant ($P = .0488$).

Sixteen weeks later, the effect endured, with 73.5% of the CP101 group and 59.4% of the placebo group still free of recurrence. The statistical significance of the difference improved slightly ($P = .0347$).

Drug-related emergent adverse events were similar between the two groups: 16.3% for the CP101 group vs. 19.2% for the placebo group. These were mostly gastrointestinal symptoms, and none was serious.

AGA Resource
Help your patients understand their *C. difficile* diagnosis by sharing patient education from the AGA GI Patient Center: www.gastro.org/Cdiff.

Some patients received vancomycin as a first-line treatment for *C. difficile* infections, and the researchers wondered if the washout period was not sufficient to purge that antibiotic, leaving enough to interfere with the effectiveness of CP101.

Therefore, they separately analyzed 40 patients treated with fidaxomicin, which they expected to wash out more quickly. Among these patients, 81% who received CP101 were free of recurrences, at 8 weeks and 24 weeks. This compared with 42.1% of those who received the placebo, at both time points. This difference was more statistically significant ($P = .0211$).

Understanding how it works

At baseline, the patients had about the same number of organisms, but after a week the diversity was greater in the patients treated with CP101, and that difference had increased at week 8. The researchers also found much less diversity of organisms in the stools of those patients who had recurrences of *C. difficile* infection.

The diversity of microbes in the successfully treated patients appeared to have been introduced by CP101. Dr. Allegretti and colleagues measured the number of organisms in the stool samples that came from CP101. They found that 96% of patients colonized by the CP101 organisms had avoided recurrence of the *C. difficile* infections, compared with 54.2% of those patients not colonized by these microbes.

The data on colonization is interesting because it has not been found with fecal microbiota transplants, said Purna Kashyap, MBBS, AGAF, codirector of the Microbiome Program at the Mayo Clinic College of Medicine in Rochester, Minn., who was not involved in the study.

But to better interpret the data, it would be helpful to know more about how the placebo and CP101 groups compared at baseline with regard to medications, immunosuppression, and antibiotics used to treat the *C. difficile* infections, Dr. Kashyap said. He was struck by the lower cure rate in the portion of the placebo group treated with fidaxomicin.

"Overall, I think these are exciting observations based on the data but require careful review of the entire data to make sense of [them], which will happen when it goes through peer review," he told this news organization in an email.

Several other standardized microbiota restoration products are under development. In contrast to CP101, which is made up of whole stool, VE303 is a "rationally defined bacterial consortium," and SER-109 is a "consortium of highly purified Firmicutes spores." VE303 has completed a phase 2 trial, and SER-109 has completed a phase 3 trial.

Dr. Allegretti is a consultant for Finch Therapeutics, which funded the trial. Dr. Kashyap has disclosed no relevant financial relationships.

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Move beyond visceral triggers

Pain *from page 1*

behavioral factors can affect the treatment of these patients, making it a complex clinical problem that calls for a collaborative approach between the patient and clinician. Opioids and other drugs that could be misused should be avoided, according to the authors. Both pharmacologic and nonpharmacologic approaches can be considered, but the update did not address use of marijuana or other complementary or alternative therapies.

Effective management requires empathy and collaboration. The patient has often seen various other clinicians with suboptimal results, which has left them dissatisfied with their care. Cultural sensitivity is crucial because the understanding and interpretation of pain, and preferred management approaches, vary across cultures.

The first step is a nonjudgmental patient history using open-ended questions. Examples include: "How do your symptoms interfere with your ability to do what you want in your daily life?" or "How are these symptoms affecting your life the most?" These types of questions may identify patients who could benefit from behavioral health interventions.

Questions about symptom-related anxiety can improve understanding of patient concerns and offer an opportunity to address fears. Additional understanding of the patient's perspective can come from questions like: "What do you think is causing your symptoms?" "Why are you coming to see me now?" and "What are you most concerned about with your symptoms?"

The initial assessment should ideally result in shared goals and expectations for pain management.

Providers should educate the patient about the pathogenesis of pain and how it can be modified. Pain signals can result from innocuous signals from the gut that are misinterpreted by the vigilant brain as it scans for injury or illness. That model might explain why some patients with similar diagnoses have widely differing pain experiences, and offers hope that a change in how one approaches pain might lead to improvements. Patients should be encouraged to avoid too much focus on the cause or a solution to pain, because it can interfere with acceptance of pain or, when needed, treatment.

Opioids should not be prescribed for these patients, and if they are already taking them on referral, it's important to manage them within a multidisciplinary framework until the opioids can be discontinued. Long-term use of opioids can lead to narcotic bowel syndrome, which results in chronic and often

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heightened abdominal pain even with escalating opioid doses. Opioid stoppage often must be accompanied by behavioral and psychiatric therapies to ensure success.

Nonpharmacological therapies such as brain-gut psychotherapies should be brought up as potential options early in treatment, even though many patients won't require this type of care. Early mention is likely to keep the patient more open to trying them because they're less likely to think of it as a sign of failure or a "last-ditch" approach.

Cognitive-behavioral therapy works to improve pain management skills and bolster skill deficits, with attention to pain catastrophizing, pain hypervigilance, and visceral anxiety through different techniques.

Gut-directed hypnotherapy deals with somatic awareness and the use of imagery and suggestion to reduce pain sensations. Mindfulness-based stress reduction has been shown to be effective in inflammatory bowel disease and musculoskeletal pain syndromes. The provider should be familiar with these available methods, but should leave choice of interventions to partner mental health providers.

It's important to distinguish between gastrointestinal pain with visceral causes and centrally mediated pain. Central sensitization can cause intermittent pain to become persistent even in the absence of ongoing peripheral causes of pain.

Peripheral acting agents affect gastrointestinal pain, and a network meta-analysis identified the top three drugs for pain relief in irritable bowel syndrome as tricyclic antidepressants, antispasmodics, and peppermint oil.

Neuromodulator drugs are an option for DGBI pain because the gut nervous system shares embryonic developmental pathways with the brain and spinal cord, which helps explains some of the benefits of low-dose antidepressants, now termed gut-brain neuromodulators. These drugs should be started at a low dose and gradually titrated according to symptom response and tolerability.

The authors have financial relationships with various pharmaceutical companies.

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Quick quiz answers

Q1. Correct answer: A. *Diphyllobothrium latum*.

Rationale

This is likely a tapeworm infection with *Diphyllobothrium latum*. *D. latum* infection can be acquired from ingesting certain forms of freshwater fish, and those who consume raw fish, including sushi, are at increased risk. The classical manifestation of infection with *D. latum* is megaloblastic anemia due to vitamin B12 deficiency. *D. latum* has a unique affinity for vitamin B12 and therefore competes with the host for absorption. Humans become infected with Taenia by ingesting raw or undercooked infected meat containing cysticerci. Infection with Hymenolepis is common in children secondary to breaches in fecal-oral hygiene. Most infections are asymptomatic.

Reference

Webb C, Cabada MM. Curr Opin Infect Dis. 2017 Oct;30(5):504-10.

Q2. Correct answer: A. Intravenous proton pump inhibitor drip.

Rationale

It is important to understand the initial management of patients with bleeding esophageal varices. With voluminous hematemesis, especially from a proximal source like the esophagus, airway protection is crucial so this patient should be intubated. Patients like this are at high risk to develop infected ascites so IV antibiotics should be given. Antibiotics have been shown to decrease mortality in cirrhotic patients admitted with GI bleeding. Somatostatin analogs decrease portal inflow by causing splanchnic vasoconstriction and have been proven to achieve hemostasis and decrease the risk of rebleeding. One has to be cautious with resuscitation efforts, as excessive resuscitation can lead to accelerated bleeding due to increased portal pressures. However, this patient's hemoglobin concentration is well below the threshold that warrants transfusion, so giving him PRBCs is appropriate. In the acute setting of an upper GI bleed, proton pump inhibitors work to help optimize platelet function by increasing gastric pH. Since the source here is varices in the more pH neutral esophageal environment, intravenous PPI likely has little effect in the acute setting. However, after band ligation is performed, it may help decrease the risk of forming post-banding ulcers. Since this patient's banding was performed a month ago, this episode of bleeding is more likely to be from recurrent varices than from a post-banding ulcer.

References

Garcia-Tsao G et al. Hepatology. 2007 Sep;46(3):922-38.

Tripathi D et al. Gut. 2015 Nov;64(11):1680-704.

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