8 • MEMBER SPOTLIGHT
Ergonomic 'Timeouts' Make Endoscopy Easier for GIs.

10 • INTESTINAL DISORDERS
Anxiety, Depression, and Insufficient Exercise Linked to IBD Flare.

20 • IN FOCUS
Practical Approach Aids Diagnosis, Management of Eosinophilic Esophagitis.

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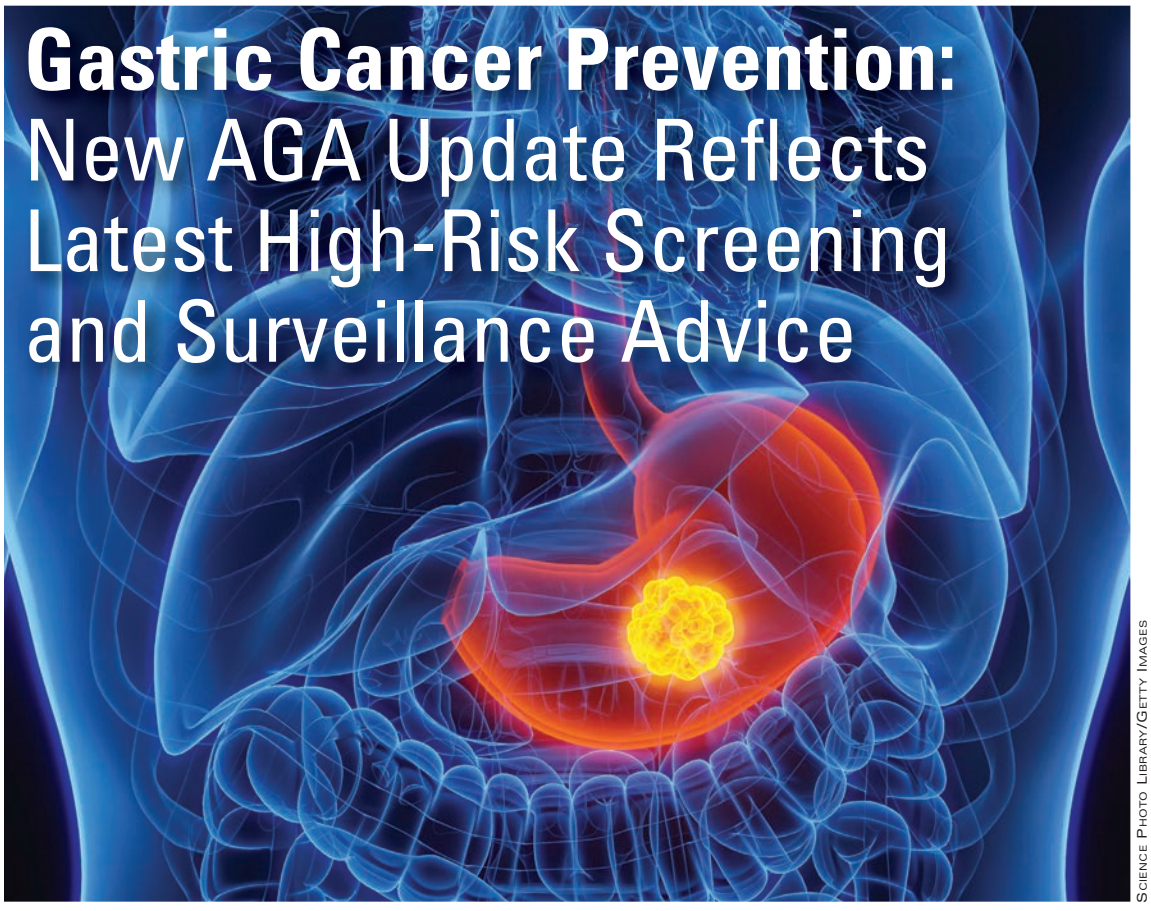
GI&Hepatology News

June 2025 Volume 19 / Number 6



Gastric Cancer Prevention: New AGA Update Reflects Latest High-Risk Screening and Surveillance Advice

SCIENCE PHOTO LIBRARY/GETTY IMAGES

BY CAROLYN CRIST

FROM GASTROENTEROLOGY

Clinicians can help reduce gastric cancer incidence and mortality in high-risk groups through endoscopic screening and surveillance of precancerous conditions, such as gastric intestinal metaplasia (GIM), according to a new clinical practice update from the American Gastroenterological Association (AGA).

The update supports additional gastric guidance published so far in 2025, including a clinical guideline on the diagnosis and management of gastric premalignant conditions (GPMC) from the American College of Gastroenterology (ACG) (2025 Mar. doi: 10.14309/ajg.0000000000003350) and upper gastrointestinal (GI) endoscopy quality indicators from ACG and the American Society for Gastrointestinal Endoscopy (ASGE) (2025 Feb. doi: 10.1016/j.gie.2024.08.023).

"The synergy of these three publications coming out at the same time helps us to finally establish surveillance of high-risk gastric conditions in practice, as we do in the colon and esophagus," said Douglas R. Morgan, MD, professor of medicine in gastroenterology and hepatology and director of global health

See **Gastric Cancer Prevention** · *page 22*

Semaglutide Therapy Improves Liver Histology in MASH

BY DIANA SWIFT

Adult patients with metabolic dysfunction–associated steatohepatitis (MASH) and moderate or advanced liver fibrosis showed improved liver histology with a once-weekly dose of semaglutide (Wegovy), an ongoing randomized placebo-controlled trial reported.

The glucagon-like peptide 1 receptor agonist (GLP-1 RA) is currently a candidate for treating MASH.

Preliminary results of the two-part phase 3, double-blind ESSENCE trial, conducted in at 253 clinical sites in 37 countries, were published in *The New England Journal of Medicine* (2025 Apr. doi: 10.1056/NEJMoa2413258).

A previous phase 2 study by Loomba et al suggested semaglutide was effective in reducing liver injury (Lancet Gastroenterol Hepatol. 2023 Mar. doi: 10.1016/S2468-1253[23]00068-7). "That study, however, did not show improvement in liver fibrosis, which this study has done," study co-lead Philip Newsome, PhD, professor in the department of immunology and immunotherapy and honorary professor of experimental hepatology at the University of Birmingham in England, said in an interview.

"The results aligned with expectations in that the impact on liver fibrosis was anticipated — but with some uncertainty, so this study is important in that regard."

See **Semaglutide Therapy** · *page 17*

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LETTER FROM THE EDITOR

An Uncertain Future for No-Cost Preventive Care

Later this month, the US Supreme Court is anticipated to announce its decision in *Kennedy vs. Braidwood Management*, a case that could significantly impact the no-cost coverage of preventive health care services under the Patient Protection and Affordable Care Act (ACA). At the center of the case is whether the structure and function of the US Preventive Services Task Force (USPSTF) — an independent body convened by the federal government that makes recommendations for preventive services that most private insurances must cover without cost-sharing under provisions of the ACA (specifically, Grade A and B recommendations) — violates the Appointments Clause of the US Constitution. The litigants claim that USPSTF does not have the authority to set coverage requirements because its members are not appointed by the President with the Senate's approval.

The case, initiated in 2022 by a self-insured, Christian-owned business, specifically targeted the coverage of pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. However, the decision could broadly affect the coverage of other preventive services, including colorectal cancer screening tests. In June 2024, the 5th Circuit Court of Appeals upheld a district court's ruling that the ACA's requirement to cover without cost-sharing services recommended by USPSTF is unconstitutional, paving the way for the current Supreme Court showdown.

The consequences of this ruling could be significant. If the Court rules in favor of Braidwood, private health insurers would no longer

Dr. Adams

If the Court rules in favor of Braidwood, private health insurers would no longer be required to cover, without cost-sharing, preventive services recommended by USPSTF.

be required to cover, without cost-sharing, preventive services recommended by USPSTF after March 2010 when the ACA was enacted. This would likely reverse some of the progress we have made in increasing CRC screening rates by reducing financial barriers to care, particularly among average risk adults aged 45-49 years (newly recommended for screening since 2010). Interestingly, despite a new administration, the federal government continues to advocate for upholding the law, asserting that USPSTF members are "inferior officers" such that the Secretary of Health & Human Services can dismiss individual members and oversee or veto the Task Force's recommendations at will, potentially threatening scientific independence. Though it's often challenging to predict the Supreme Court's final ruling, the tone of questioning during oral arguments in April hinted at a possible win for the ACA and preventive care. Stay tuned, as the decision to be released later this month has seismic clinical implications. ■

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

Member SPOTLIGHT
See page 8

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

GI & Hepatology News (ISSN 1934-3450) is published monthly for $230.00 per year by Frontline Medical Communications Inc., 283-299 Market Street (2 Gateway Building), 4th Floor, Newark, NJ 07102. Phone 973-206-3434

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Short-Term Elemental Diet Eases Symptoms in Microbiome Gastrointestinal Disorders

BY HEIDI SPLETE

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Short-term adherence to a palatable elemental diet (PED) significantly improved symptoms and the gut microbiota in adults with microbiome-driven gastrointestinal disorders, according to a new study.

"Elemental diets have long shown promise for treating gastrointestinal disorders like Crohn's disease, eosinophilic esophagitis, SIBO [small intestinal bacterial overgrowth], and IMO [intestinal methanogen overgrowth], but poor palatability has limited their use," lead author Ali Rezaie, MD, medical director of the Gastrointestinal (GI) Motility Program and director of bioinformatics at Cedars-Sinai Medical Center, Los Angeles, told *GI & Hepatology News*.

Dr. Rezaie

Elemental diets are specialized formulas tailored to meet an individual's specific nutritional needs and daily requirements for vitamins, minerals, fat, free amino acids, and carbohydrates.

In SIBO and IMO specifically, only about half the patients respond to antibiotics, and many require repeat treatments, which underscores the need for effective nonantibiotic alternatives, said Rezaie. "This is the first prospective trial using a PED, aiming to make this approach both viable and accessible for patients," he noted.

Assessing a Novel Diet in IMO and SIBO

In the study, which was recently published in *Clinical Gastroenterology and Hepatology* (2025 Apr 4. doi: 10.1016/j.cgh.2025.03.002), Rezaie and colleagues enrolled 30 adults with IMO (40%), SIBO (20%), or both (40%). The mean participant age was 45 years, and 63% were women.

All participants completed 2 weeks of a PED, transitioned to 2-3 days of a bland diet, and then resumed their regular diets for 2 weeks.

The diet consisted of multiple 300-calorie packets, adjusted for individual caloric needs. Participants could consume additional packets for hunger but were prohibited from eating other foods. There was no restriction on water intake.

The primary endpoint was changes in stool microbiome after the PED and reintroduction of regular food. Secondary endpoints included lactose breath test normalization to determine bacterial overgrowth in the gut, symptom response, and adverse events.

Researchers collected 29 stool samples at baseline, 27 post PED, and 27 at study conclusion (2 weeks post diet).

Key Outcomes

Although the stool samples' alpha diversity decreased after the PED, the difference was not statistically significant at the end of the study. However, 30 bacterial families showed significant differences in relative abundance post PED.

Daily symptom severity improved significantly during the second week of the diet compared with baseline, with reduction in abdominal discomfort, bloating, distention, constipation, and flatulence. Further significant improvements in measures such as abdominal pain, diarrhea, fatigue, urgency, and brain fog were observed after reintroducing regular food.

"We observed 73% breath test normalization and 83% global symptom relief — with 100% adherence and tolerance to 2 weeks of exclusive PED," Rezaie told *GI & Hepatology News*. No serious adverse events occurred during the study, he added.

Lactose breath test normalization rates post PED were 58% in patients with IMO, 100% in patients with SIBO, and 75% in those with both conditions.

The extent of patient response to PED was notable, given that 83% had failed prior treatments, Rezaie said.

"While we expected benefit based on palatability improvements and prior retrospective data, the rapid reduction in methane and hydrogen gas — and the sustained microbiome modulation even after reintroducing a regular diet — exceeded expectations," he said. A significant reduction in visceral fat was another novel finding.

THINKSTOCK

"This study reinforces the power of diet as a therapeutic tool," Rezaie said, adding that the results show that elemental diets can be palatable, thereby improving patient adherence, tolerance, and, eventually, effectiveness. This is particularly valuable for patients with SIBO and IMO who do not tolerate or respond to antibiotics, prefer nonpharmacologic options, or experience recurrent symptoms after antibiotic treatment.

Dr. Roper

Limitations and Next Steps

Study limitations included the lack of a placebo group with a sham diet, the short follow-up after reintroducing a regular diet, and the inability to assess microbial gene function.

However, the results support the safety, tolerance, and benefit of a PED in patients with IMO/SIBO. Personalized dietary interventions that support the growth of beneficial bacteria may be an effective approach to treating these disorders, Rezaie and colleagues noted in their publication.

Although the current study is a promising first step, longer-term studies are needed to evaluate the durability of microbiome and symptom improvements, Rezaie said.

Making the Most of Microbiome Manipulation

Elemental diets may help modulate the gut microbiome while reducing immune activation, making them attractive for microbiome-targeted gastrointestinal therapies, Jatin Roper, MD, a gastroenterologist at Duke University, Durham, North Carolina, told *GI & Hepatology News*.

"Antibiotics are only effective in half of SIBO cases and often require retreatment, so better therapies are needed," said Roper, who was not affiliated with the study. He added that its findings confirmed the researchers' hypothesis that a PED can be both safe and effective in patients with SIBO.

Roper noted the 83% symptom improvement as the study's most unexpected and encouraging finding, as it represents a substantial improvement compared with standard antibiotic therapy. "It is also surprising that the tolerance rate of the elemental diet in this study was 100%," he said.

However, diet palatability remains a major barrier in real-world practice.

"Adherence rates are likely to be far lower than in trials in which patients are closely monitored, and this challenge will not be easily overcome," he added.

The study's limitations, including the lack of metagenomic analysis and a placebo group, are important to address in future research, Roper said. In particular, controlled trials of elemental diets are needed to determine whether microbiome changes are directly responsible for symptom improvement.

The study was supported in part by Good LFE and the John and Geraldine Cusenza Foundation. Rezaie disclosed serving as a consultant/speaker for Bausch Health and having equity in Dieta Health, Gemelli Biotech, and Good LFE. Roper had no financial conflicts to disclose. ■

Member SPOTLIGHT

Ergonomic 'Timeouts' Make Endoscopy Easier for GIs

BY JENNIFER LUBELL
MDedge News

Amandeep Shergill, MD, MS, AGAF, always thought she had good hand-eye coordination until she entered her gastroenterology (GI) fellowship.

"You're learning how to scope and the endoscope just feels so awkward in the hands. It can be such a difficult instrument to both learn and to use," said Shergill, professor of clinical medicine at University of California, San Francisco.

Her attendings and mentors couldn't give her the feedback she needed.

"I was told that I wasn't holding it right. But every time I tried to do something that someone was trying to tell me, it seemed like my hands were too small. I couldn't hold it the way that they were teaching me to hold it." She began to wonder: Was this about her or the tool itself?

A deep dive into hand tool interactions and medical device designs led her to human factors and ergonomics. Her fellowship mentor, Ken McQuaid, MD, AGAF, had gone to medical school with David Rempel, MD, MPH, who was one of the top-funded ergonomists in the country. "He emailed David and wrote: I have a fellow who's interested in learning more about ergonomics and applying it to endoscopy," said Shergill.

Through her work with Rempel, she was able to uncover the mechanisms that lead to musculoskeletal disorders in endoscopists.

Over time, she has become a trailblazer in this field, helming the UC Berkeley Center for Ergonomic Endoscopy with Carisa Harris-Adamson PhD, CPE, her ergonomics collaborator. In an interview, she described the unique "timeout" algorithm she created to ease the process of endoscopy for GI physicians.

What is your favorite aspect of being a GI physician?

I really love the diversity of patients and cases. You're always learning something new. It's an internal medicine subspecialty and a cognitive field, so we must think about differential diagnoses, risks and benefits of procedures for patients. But as a procedural field, we get to diagnose and immediately treat certain disorders. What's exciting about GI right now is there's still so much to learn. I think that we're still discovering more about how the brain-gut interaction works every day. There's been additional research about the microbiome and the immense influence it has on both health and disease. The field is continuing to evolve rapidly. There's always something new to learn, and I think it keeps us fresh.

Tell me about your work in ergonomics and endoscopy.

Ken McQuaid connected me with David Rempel. I worked with David to approach this problem of endoscopy ergonomics from a very rigorous ergonomics perspective. Early in my fellowship, endoscopy ergonomics wasn't well known. There were few survey-based studies, including one from the American Society for Gastrointestinal Endoscopy [ASGE] that documented a high prevalence of endoscopist injury. But not a lot was known about what was causing injury in endoscopists.

What were the risk factors for endoscopist injury? Instead of just doing another survey, I wanted to show that there was this potential for causation given the design of the endoscopes. I worked with David to do a pilot study where we collected some pinch forces and forearm muscle loads. I was able to collect some pilot data that I used to apply for the ASGE Endoscopic Research Award. And luckily, ASGE supported that work.

Another award I received, the ASGE Career Development Award, was instrumental in allowing me to become more proficient in the science of ergonomics. I was able to leverage that career development award to go back to school. I went to UC Berkeley and got a master's in environmental health sciences with a focus on ergonomics. It really helped me to lay the foundation and understanding for ergonomics and then apply that to endoscopy to generate a more rigorous scientific background for endoscopy ergonomics and start that conversation within the field of GI.

What leads to musculoskeletal disorders in endoscopists and how can it be prevented?

Musculoskeletal disorders are associated with the repetitive procedures that we're performing, often utilizing high forces and in non-neutral postures. This is because of how we're interacting with our tools and how we're interacting with our environments. The studies I have done with Carisa Harris-Adamson have been able to demonstrate and document the high forces that are required to interact with the endoscope. To turn the control section dials and to torque and manipulate the insertion tube, there are really high distal upper extremity muscle loads that are being applied.

We were able to compare the loads and the forces we were seeing to established risk thresholds from the ergonomics literature and demonstrate that performing endoscopy was associated with moderate to high risk of development of distal upper extremity disorders.

What research are you doing now?

We're trying to focus more on interventions. We've done some studies on engineering controls we can utilize to decrease the loads of holding the scope. First, it was an anti-gravity support arm. More recently we're hoping to publish data on whether a scope stand can alleviate some of those left distal upper extremity loads because the stand is holding the scope instead of the hand holding the scope. Can we decrease injury risk by decreasing static loading?

Neck and back injuries, which have a high prevalence in endoscopists, are usually associated with how the room is set up. One of the

Continued on following page

Courtesy Dr. Amandeep Shergill

Amandeep Shergill, MD, MS, AGAF, is a trailblazing endoscopist and professor of clinical medicine at the University of California, San Francisco.

Lightning round

Coffee or tea?
Coffee

Favorite book?
Project Hail Mary (audiobook)

Beach vacation or mountain retreat?
Mountain retreat

Early bird or night owl?
Night owl

Go-to comfort food?
Chaat (Indian street food)

Dogs or cats?
Dogs

Hobby you'd like to pick up?
Sewing

Historical figure you wish to join for dinner?
Ruth Bader Ginsburg

Go-to karaoke song?
I Wanna Dance With Somebody

One thing on your bucket list?
To see the Northern Lights

Continued from previous page

things that I've tried to help promote is a pre-procedure ergonomic "timeout." Before an endoscopist does a procedure, we're supposed to perform a timeout focused on the patient's safety. We should also try to advocate for physician safety and an ergonomic timeout. I developed a mnemonic device utilizing the word "MYSELF" to help endoscopists remember the ergonomic timeout checklist: M = monitor, Y = upside-down Y stance, S = scope, E = elbow/ bed position, L = lower extremities, F = free movement of endoscope/ processor placement.

First, thinking about the monitor, "M," and fixing the monitor height so that the neck is in neutral position. Then, thinking of an upside down "Y" standing straight with the feet either hip width or shoulder width apart, so that the physician has a stable, neutral standing posture. Then "S" is for checking the scope to ensure you have a scope with optimal angulation that's working properly.

"E" is for elbows — adjusting the bed to an optimal position so that elbows and shoulders are in neutral position. "L" is for lower extremities — are the foot pedals within an easy reach? Do you have comfortable shoes on, an anti-fatigue floor mat if you need it? And then the "F" in "MYSELF" is for the processor placement, to ensure "free movement" of the scope. By placing the processor directly behind you and lining up the processor with the orifice to be scoped, you can ensure free movement of the scope so that you can leverage large movements of the control section to result in tip deflection.

We studied the MYSELF mnemonic device for a pre-procedure ergonomic timeout in a simulated setting and presented our results at Digestive Disease Week® (DDW) 2024, where we showed a reduction in ergonomic risk scores based on the Rapid Entire Body Assessment tool.

We presented the results of the scope stand study at DDW 2025 in San Diego this May.

COURTESY DR. AMANDEEP SHERGILL

Dr. Amandeep Shergill is a proponent of work-life balance. She says GIs should create boundaries to prioritize things in their personal and professional lives.

What has been the feedback from physicians who use these supportive tools?

While physicians are very grateful for bringing attention to this issue, and many have found utility in some of the tools that I proposed, I think we still have so much work to do. We're just all hoping to continue to move this field forward for better tools that are designed more with the breadth of endoscopists in mind.

How do you handle stress and maintain work-life balance?

A few years ago, during DDW I gave a talk entitled "Achieving Work-Life Harmony." I disclosed at the beginning of the talk that I had not achieved work-life harmony. It's definitely a difficult thing to do, especially in our field as GI proceduralists, where we're frequently on call and there are potentially on-call emergencies.

One of the key things that I've tried to do is create boundaries to prioritize both things in my personal life and my professional life and really try to stay true to the things that are important to me. For instance, things like family time and mealtimes, I think that's so critical. Trying to be home on evenings for dinnertime is so important.

One of my GI colleagues, Raj Keswani, MD, MS, gave a talk about burnout and described imagining life as juggling balls; trying to figure out which balls are glass balls and need to be handled with care, and which balls are rubber balls.

More often, work is the rubber ball. If you drop it, it'll bounce back and the work that you have will still be there the next day. Family, friends, our health, those are the glass balls that if they fall, they can get scuffed or shatter sometimes. That image helps me think in the moment. If I need to decide between two competing priorities, which one will still be here tomorrow? Which is the one that's going to be more resilient, and which is the one that I need to focus on? That's been a helpful image for me.

I also want to give a shout out to my amazing colleagues. We all pitch in with the "juggling" and help to keep everyone's "balls" in the air, and cover for each other. Whether it's a sick patient or whatever's going on in our personal lives, we always take care of each other.

What advice would you give to aspiring GI fellows or graduating fellows?

GI is such an amazing field and many people end up focusing on the procedural aspect of it. What I think defines an exceptional gastroenterologist and physician in general is adopting both a "growth mindset" and a "mastery mindset." I would really encourage GI fellows to lean into that idea of a mastery mindset, especially as they're identifying that niche within GI that they may be interested in pursuing. And really, it starts out with when you're exploring an area of focus, listening to what consistently draws your attention, what you're excited about learning more about.

Finding mentors, getting involved in projects, doing deep learning, and really trying to develop an expertise in that area through additional training, coursework, and education. I think that idea of a mastery mindset will really help set you up for becoming deeply knowledgeable about a field. ■

Anxiety, Depression, and Insufficient Exercise Linked to IBD Flare

BY LIAM DAVENPORT

FROM ECCO 2025

BERLIN — Psychosocial factors, such as anxiety and depression, are associated with an increased risk for both self-reported "clinical" and symptomatic, or "hard," flare in inflammatory bowel disease (IBD), suggested a study of UK patients.

The research was presented at the European Crohn's and Colitis Organisation (ECCO) 2025 Congress.

"Despite clinical remission, there is a significant burden of psychosocial comorbidity in IBD patients," said study presenter Lauranne A.A.P. Derikx, PhD, a gastroenterology researcher at Erasmus University MC, Rotterdam, the Netherlands.

"Anxiety, sleep, and somatization were associated with an increased risk of clinical flare, and depression and lack of exercise were associated with an increased risk of hard flare," she said. "Altogether, this supports a holistic approach in IBD patients."

Stephen E. Lupe, PsyD, director of behavioral medicine for the department of gastroenterology, hepatology and nutrition at the Cleveland Clinic, Ohio, who was not involved in the study, agreed.

"Whole-person care is so important" in IBD, and this study is part of a growing literature making the connection between symptom flare and factors such as anxiety, depression, stress, and even trauma, he said in an interview.

Searching for Predictive Links

The relapsing and remitting disease course in IBD is dynamic and hard to predict, Derikx said. Unfortunately, clinicians don't know which patients with IBD will develop a flare or when it will occur.

There's a high prevalence of psychosocial comorbidity among patients with IBD and a "bidirectional relationship between psychosocial vulnerabilities" and the disease course via the gut-brain axis, Derikx noted.

To determine which psychosocial factors may be associated with and predictive of IBD flare, researchers analyzed data from the PREdiCCt study, a large prospective study of patients with IBD from 47 centers across the United Kingdom that aims to determine the factors associated with developing a flare.

The median age of PREdiCCT study participants was 44 years, median duration of IBD was 10 years, and 35% were receiving advanced IBD therapy. The median fecal calprotectin level was 49 mcg/g, although 18% of patients had a level > 250 mcg/g, Derikx noted.

"Anxiety, sleep, and somatization were associated with an increased risk of clinical flare, and depression and lack of exercise were associated with an increased risk of hard flare."

To be included in PREdiCCT, patients must have received the diagnosis of IBD more than 6 months previously, not changed their medication for more than 2 months, and answered "yes" to the question: Do you think your disease has been well controlled in the past 1 month? The question was chosen as a measure of clinical remission.

The team collected stool samples and gathered information via questionnaires about lifestyle, diet, and other factors.

Depression and Anxiety Increase Risk

Researchers included 1641 patients — 830 with Crohn's and 811 with ulcerative colitis or IBD unclassified (IBDU) — with complete datasets in their analysis of associations between psychosocial factors and IBD flare.

Baseline questionnaires identified moderate anxiety in 18.8% of participants, severe anxiety in 16.1%, moderate depression in 9.8%, severe depression in 5.7%, sleep disturbances in 46.4%, moderate somatization in 22.8%, severe somatization in 7.9%, insufficient exercise in 22.2%, and consumption of more than 14 units of alcohol in 24%.

After 24 months of follow-up, 36% of patients had experienced a clinical flare, defined as answering "no" to the question: Do you think your disease has been well controlled in the past 1 month/since you last logged in to the [study] portal?

In addition, 13% of patients experienced a hard flare, defined as a clinical flare plus C-reactive protein levels > 5 mg/L and/or a calprotectin level > 250 mcg/g and a change in IBD therapy.

Survival analyses with Cox frailty models adjusted for baseline fecal calprotectin, sex, index of multiple deprivation, hospital site, and patient age revealed statistically significant associations between several psychosocial factors and increased risk for flare.

Moderate anxiety in Crohn's disease increased clinical flare risk (adjusted hazard ratio [aHR], 1.64), as did severe anxiety in both Crohn's disease (aHR, 1.86) and ulcerative colitis/IBDU (aHR, 1.46). Moderate depression and severe depression increased the flare risk in ulcerative colitis/IBDU (aHR, 1.72 and 1.67, respectively). Also increasing clinical flare risk was poor sleep quality in Crohn's disease (aHR, 1.58), and severe somatization in Crohn's disease (aHR, 3.86) and ulcerative colitis/IBDU (aHR, 1.96).

Dr. Lupe

Fewer psychosocial factors were associated with increased risk for hard flare: moderate depression in ulcerative colitis/IBDU (aHR, 2.5), severe somatization in Crohn's disease (aHR, 2.34), and lack of exercise in ulcerative colitis/IBDU (aHR, 1.55).

Physician-Patient Disconnect

There is "very little correlation" between self-reported and symptomatic flare in IBD, Lupe said. "This happens all the time, where the gastroenterologist will come out of the endoscopy suite and go: 'You're in remission.' And the patient goes: 'What are you talking about? I'm still going to the bathroom 20 times a day.' "

Now there are data showing that, if the care team undertakes behavioral work with patients who have IBD, "the medications work more effectively," Lupe said.

"I think medicine is in a point of transition right now," he added. "We're (moving from) looking at people as disease states and 'how do I treat the disease' to 'how do I take care of this human being,' knowing that everything this human being does, including everything we put in our mouth, everything we experience, changes what happens inside our body, and it's measurable."

"Whole-person care is so important" in IBD, and this study is part of a growing literature making the connection between symptom flare and factors such as anxiety, depression, stress, and even trauma.

The PREdiCCt study is sponsored by the University of Edinburgh, Scotland. Derikx declared relationships with AbbVie, Janssen Pharmaceuticals, Sandoz, Galapagos, and Pfizer. Other authors also declared relationships with pharmaceutical companies. ■

Backbone of MASH Treatment?

Semaglutide Therapy *from page 1*

Study Details

From May 2020 to April 2023, researchers led by Newsome and Arun J. Sanyal, MBBS, MD, of Stravitz-Sanyal Institute for Liver Disease and Metabolic Health at Virginia Commonwealth University School of Medicine, Richmond, randomized 1197 patients with a mean age of 56 years. Of these, 57% were women and 67.5% were White individuals. Mean body mass index was 34.6, and 55.9% had type 2 diabetes.

Dr. Newsome

All had biopsy-defined MASH and fibrosis stage 2 or 3 according to the Nonalcoholic Steatohepatitis Clinical Research Network classification (Hepatology. 2005 Jun;41[6]:1313-1321) and a Nonalcoholic Fatty Liver Disease Activity Score ≥ 4 (Hepatology. 2011 Mar;53[3]:810-820).

Rates of fibrosis were 31.3% for stage 2 fibrosis and 68.8% for stage 3. Diverse geographic site locations included Asia (25.1%), Europe (25.3%), North America (35.0%), and South America (7.9%), and others (6.8%).

The histologic benefits of semaglutide also emerged in improvements on all prespecified noninvasive tests — including aspartate transaminase and alanine transaminase levels and liver stiffness.

In a 2:1 ratio, they were assigned to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 240 weeks. A planned interim analysis of the first 800 patients was done at week 72, with primary endpoints being resolution of steatohepatitis without worsening of liver fibrosis and reduction in liver fibrosis without worsening of steatohepatitis.

Resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of the 534 patients in the semaglutide group and in 34.3% of the 266 patients in the placebo group (estimated difference, 28.7 percentage points; 95% CI, 21.1-36.2, $P < .001$).

A reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of semaglutide recipients and 22.4% of placebo recipients (estimated difference, 14.4 percentage points; 95% CI, 7.5-21.3, $P < .001$).

In secondary findings, the combined resolution of steatohepatitis and reduction in liver fibrosis was reported in 32.7% in the semaglutide group vs 16.1% in the placebo group (estimated difference, 16.5 percentage points; 95% CI, 10.2-22.8; $P < .001$).

The mean change in body weight was –10.5% with semaglutide and –2.0% with placebo (estimated difference, –8.5 percentage points; 95% CI, –9.6 to –7.4, $P < .001$). Mean changes in bodily pain scores did not differ significantly between arms.

Dr. Chalasani

The histologic benefits of semaglutide also emerged in improvements on all prespecified noninvasive tests — including aspartate transaminase and alanine transaminase levels and liver stiffness. Emerging evidence has suggested an association between reductions in liver stiffness and clinical benefit (JAMA. 2024;331[15]:1287-1297).

Gastrointestinal adverse events were more common in the semaglutide group.

Commenting on the study from a nonparticipant's perspective, Naga P. Chalasani, MD, AGAF, professor of gastroenterology and hepatology at Indiana University School of Medicine, Indianapolis, said results from the ESSENCE trial were "long awaited and they certainly advance the field of MASH clinical trials substantially."

Furthermore, he added, the results are well aligned with those of a phase 2b trial of semaglutide by Newsome and colleagues for what was then termed nonalcoholic steatohepatitis (N Engl J Med. 2020 Nov. doi: 10.1056/NEJMoa2028395), and "they also align with what is known about the positive role of incretins, digestive hormones imitated by GLP-1s to improve liver health in patients with ... MASH."

"The results from this study certainly make a case for semaglutide to be the backbone therapy for diabetic or obese patients with MASH and fibrosis."

"The results from this study certainly make a case for semaglutide to be the backbone therapy for diabetic or obese patients with MASH and fibrosis," Chalasani said. "More than 80% of patients with MASH and fibrosis have either diabetes and/or obesity."

He added that a better understanding is needed of how semaglutide works in patients with MASH cirrhosis since the previous small study was unsuccessful. "But this may need to be repeated as the published study was underpowered. Outcomes in the ESSENCE trial will help to clarify whether semaglutide will improve clinical outcomes beyond improving liver histology."

According to Newsome, GLP-1s will become the backbone of therapy in MASH given their range of metabolic and liver benefit. But questions remain, he said. "Will there be further improvements with longer treatment with semaglutide? What noninvasive tests should we use to determine treatment success? Which patients will benefit from combination treatment?"

This study was supported by Novo Nordisk, the manufacturer of Wegovy. Sanyal reported having various financial relationships with multiple private-sector companies, including Novo Nordisk. Newsome reported consulting for Novo Nordisk and Boehringer Ingelheim. Several study coauthors reported having similar relationships with pharmaceutical companies or employment with Novo Nordisk. Chalasani declared being involved in several MASH clinical trials conducted by other pharmaceutical companies. ■

IgG-Guided Elimination Diet Beats Sham Diet for IBS

BY DIANA SWIFT

FROM GASTROENTEROLOGY

An irritable bowel syndrome (IBS) elimination diet based on a novel IBS-specific immunoglobulin G (IgG) was superior to a sham diet for abdominal pain, an eight-center, randomized double-blind controlled trial found.

While elimination diets can provide a personalized approach to dietary therapy, existing studies have had serious methodological issues, noted lead author Prashant Singh, MBBS, of the division of gastroenterology and hepatology, department of internal medicine, Michigan Medicine, Ann Arbor, and colleagues in *Gastroenterology* (2025 Jan. doi: 10.1053/j.gastro.2025.01.223).

For example, previous studies on IgG-based diets used assays developed without determining IBS trigger foods or establishing a 95% confidence interval–based cutoff using a healthy control comparison group.

Study Details

From June 2018 to December 2021, 238 IBS patients testing positive for at least 1 food on 18-food IgG ELISA (enzyme-linked immunosorbent assay) testing and an average daily abdominal pain intensity (API) score of 3.0-7.5 on an 11.0-point scale during a 2-week run-in period were randomized for 8 weeks to an experimental antibody-guided diet or to a sham diet. The primary outcome was a 30% decrease in API for 2 of the last 4 weeks of treatment.

The overall study population had a mean age of about 40 years, and more than three quarters were female. The three IBS types — constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and mixed bowel habits-predominant (IBS-M) — accounted for about a third each in both arms.

The experimental diet eliminated foods based on a positive ELISA result. Its sham counterpart had the same number of foods removed as the number of positive-testing food sensitivities, but the foods eliminated in the sham diet had tested negative on the IgG assay.

Participants reported daily API, bloating, and stool consistency and frequency. They also reported dietary compliance and daily medication use.

Of the 238 randomized adults, 223 were included in the modified intention-to-treat analysis. A significantly greater proportion of subjects in the experimental group met the primary outcome than those in the sham group: 59.6% vs 42.1%, $P = .02$). "This highlights the potential effectiveness of a personalized elimination diet based on a novel IBS-specific IgG assay," the authors wrote.

Symptom improvement between arms began to separate out at around 2 weeks, suggesting the effect of the experimental diet was relatively rapid in onset, and continued for at least 8 weeks. The durability of response, however, needs to be assessed in future studies "and it is unclear if there is a role for repeat IgG testing to monitor treatment response," the authors wrote.

Subgroup analysis revealed that a higher proportion of those with IBS-C and IBS-M in the experimental diet group met the primary endpoint vs the sham group: 67.1% vs 35.8% and 66% vs 29.5%, respectively.

Interestingly, more patients in the experimental arm were noncompliant with their diet. "It is possible that subjects found the experimental diet more difficult to comply with compared with the sham diet or that because the experimental diet was more likely to improve symptoms, dietary indiscretion may have been more common in this group (a phenomenon seen with other elimination diets such as gluten-free diet in celiac disease)," the authors wrote.

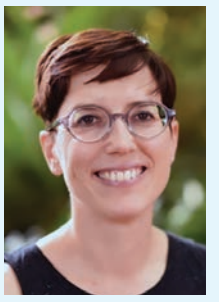
Adverse events, deemed unrelated to either regimen, were three in the experimental arm vs eight in the sham arm, which had two urinary tract infections.

The authors called for a larger, adequately powered study to assess the efficacy of an elimination diet based on this novel immunoglobulin G assay in patients with IBS-C and IBS-M. Future studies should perform detailed adherence assessments using food diaries.

"Mechanisms of how immunoglobulin G-antibody response to food antigen generates symptoms in irritable bowel syndrome are not well understood. Delineating this might provide new insights into food-related irritable bowel syndrome pathophysiology," they concluded.

This study was funded by Biomerica.

Symptoms in most people with irritable bowel syndrome (IBS) are perceived to be closely linked to diet. The low–fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet has been pivotal for the treatment of IBS, and a range of other diet approaches are now on the research horizon.



Dr. Staudacher

Whilst immunoglobulin (Ig) E–mediated allergy is relatively rare, research has suggested a role of IgG-mediated food sensitivity in causing symptoms in IBS, although the role of IgG testing and dietary elimination has been controversial. Singh and colleagues suggest an IgG-based elimination diet could improve abdominal pain and global symptoms in two thirds of people with Rome IV IBS. Critically, the study is one of the largest so far and provides the most robust and detailed description of the trial diets to date.

The potential of a new diet approach is extremely appealing, especially as the low FODMAP diet is not universally effective. However, there is still work to be done to transition the IgG-based elimination diet into guidelines and routine practice. Notably, some common foods restricted in IgG-based elimination diets are also high in FODMAPs leaving questions about the true driver of symptom benefit. Should convincing mechanistic studies and further additional trial data validate these findings, this could present a major step forward for personalized nutrition in IBS.

Heidi Staudacher, PhD, is associate professor in the School of Translational Medicine, Monash University, Melbourne, Australia. She declared no conflicts of interest.

Histamine Pathway a Target for Erythropoietic Protoporphyria?

BY DIANA SWIFT

FROM CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

An experimental study in zebrafish has suggested the decades-old, first-generation antihistamine chlorcyclizine and/or other antihistamines may be a strategy for treating erythropoietic protoporphyria (EPP)–associated liver disease by decreasing hepatic protoporphorin IX (PP-IX) accumulation.

Currently, liver transplantation is the primary treatment for this rare, painful, and life-threatening genetic disease, which is caused by excessive PP-IX accumulation and affects about 4000 people in the United States.

The findings could eventually lead to a simpler treatment that prevents hepatic damage at a much earlier stage, according to researchers led by M. Bashr Omary, MD, PhD, a professor in the Center for Advanced Biotechnology and Medicine and Robert Wood Johnson Medical School at Rutgers University in Piscataway, New Jersey.

Reporting in *Cellular and Molecular Gastroenterology and Hepatology* (2025 Jan. doi: 10.1016/j.jcmgh.2025.101463), the investigators found that chlorcyclizine reduced PP-IX levels. EPP is caused by mutations leading to deficiency of the enzyme ferrochelatase, which inserts iron into PP-IX to generate heme. The resulting condition is characterized by PP-IX accumulation, skin photosensitivity, cholestasis, and end-stage liver disease. "Despite available drugs that address photosensitivity, the treatment of EPP-related liver disease remains an unmet need," Omary and colleagues wrote.

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The Study

In order to trigger PP-IX overproduction and accumulation, the investigators administered delta-aminolevulinic acid and deferoxamine to zebrafish. These freshwater tropical fish share many physiological characteristics with humans and have been used to model human disease and develop drugs. Furthermore, these fish are transparent at the larval stage, allowing quantification and visualization of porphyrin, which is fluorescent.

The researchers had screened some 2500 approved and bioactive compounds and identified chlorcyclizine as a potent PP-IX–lowering agent.

High-throughput compound screening of ALA + DFO-treated zebrafish found that the HH-1 blocker reduced zebrafish liver PP-IX levels. The effect of chlorcyclizine was validated in porphyrin-loaded primary mouse hepatocytes, transgenic mice, and mice fed the porphyrinogenic compound 3,5-diethoxycarbonyl-1,4-dihydrocollidine.

Plasma and tissue PP-IX were measured by fluorescence; livers were analyzed by histology, immunoblotting, and quantitative polymerase chain reaction.

Chlorcyclizine-treated zebrafish larvae as well as the two types of mice all showed reduced hepatic PP-IX levels compared with controls. While the neurotransmitter played an important role in PP-IX accumulation in porphyrin-stressed hepatocytes, blockading notably decreased PP-IX levels.

Detailed analysis showed that chlorcyclizine appeared to work through multiple mechanisms, helping the liver clear toxic porphyrin buildup and reducing inflammation. It also decreased the presence of histamine-producing mast cells. The result was less liver injury, decreased porphyrin-triggered protein aggregation and oxidation, and increased clearance of PP-IX in stool.

Interestingly, in both mouse models, chlorcyclizine lowered PP-IX levels in female but not male mice in liver, erythrocytes, and bone marrow. This sex-specific effect appeared to be related to the greater speed at which male murines metabolize the drug, the authors explained in a news release. In rats, for example, the metabolism of chlorcyclizine is eight times higher in male than in female livers.

The investigators plan to launch a clinical trial in EPP patients to evaluate the effectiveness of chlorcyclizine for both liver and skin involvement. And a phase 2 trial is already underway testing the antacid cimetidine for treating EPP skin manifestations. It is possible that the different antihistamines may act additively or synergistically.

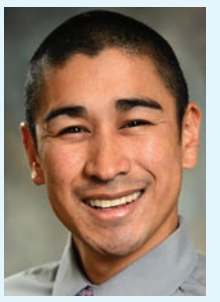
This work was supported by National Institutes of Health (NIH) grants and the Henry and Mala Dorfman Family Professorship of Pediatric Hematology/Oncology.

Omary is a member of the NIH/National Institute of Diabetes and Digestive and Kidney Diseases Data and Safety Monitoring Board of the Porphyrias Consortium.

A provisional patent application has been submitted for the use of histamine-1 receptor blockers with or without receptor blockers to treat protoporphyrias associated with PP-IX accumulation. ■

Mutations in the ferrochelatase (FECH) gene cause erythropoietic porphyria (EPP). EPP is characterized biochemically by liver and bone marrow accumulation of protoporphyrin-IX (PP-IX), and is characterized clinically by hepatic dysfunction with progression in 1%-4% to advanced liver disease.

A recent study by Kuo and colleagues exemplifies a bench-to-bedside evolution comprising pharmacological screening, mechanistic dissection, and ultimately translation of this mechanism to human subjects to treat EPP. They utilized high-throughput compound screening in a zebrafish model to identify the anti-histamine, chlorcyclizine (CCZ), as a candidate EPP therapy. CCZ lowered hepatocyte PP-IX in multiple EPP models by blocking peripheral histamine production, and by inducing hepatocyte PP-IX efflux. The data represent advances in the realms of both clinical therapeutics and molecular pathophysiological discovery.



Dr. DeBosch

From a discovery standpoint, strategic compound screening that utilizes the LOPAC (library of pharmaceutically active compounds) and Prestwick libraries offers at least two key characteristics. First, these compounds have largely known targets. The known pharmacology of chlorcyclizine provided immediate clues to validate mechanism rapidly in hepatic EPP, a relatively poorly understood disease. Moreover, screening libraries comprising Food and Drug Administration (FDA)–approved drugs can minimize lag time between discovery and translation to interventional trials in human subjects.

Beyond such strategic discovery considerations, perhaps more exciting is the therapeutic potential for anti-histaminergic therapy to mitigate hepatic manifestations in EPP. Specifically, other porphyrias with hepatic complications have FDA-approved treatments, such as anti-ALAS1 siRNAs to treat acute hepatic porphyria. No such treatment currently exists for liver dysfunction in EPP, yet CCZ and other histamine-1 (H1) receptor blockers hold such promise. Indeed, the H1 inhibitor, cimetidine, is currently in an active phase 2 trial to treat EPP (NCT05020184).

Given the already widespread use of antihistamines to symptomatically treat cutaneous EPP, we may not be too distant from pivoting and deploying readily available H1 inhibitors like cimetidine to treat EPP liver manifestations as well. Given recent data by Kuo and colleagues, such an outcome should not be too far-FECHed.

Brian DeBosch, MD, PhD, is center director of the nutrition & molecular metabolism research program, in the division of gastroenterology, hepatology & nutrition at Indiana University School of Medicine, Indianapolis. He declares no conflicts of interest.

INDEX OF ADVERTISERS

A Practical Approach to Diagnosis and Management of Eosinophilic Esophagitis

BY EVAN S. DELLON, MD, MPH, AGAF

Eosinophilic esophagitis (EoE) can be considered a "young" disease, with initial case series reported only about 30 years ago. Since that time, it has become a commonly encountered condition in both emergency and clinic settings. The most recent prevalence study estimates that 1 in 700 people in the United States have EoE,[1] the volume of EoE-associated emergency department visits trip-led between 2009 and 2019 and is projected to double again by 2030,[2] and "new" gastroenterologists undoubtedly have learned about and seen this condition. As a chronic disease, EoE necessitates longitudinal follow-up and optimization of care to prevent complications. With increasing diagnostic delay, EoE progresses in most, but not all, patients from an inflammatory- to fibrostenotic-predominant condition.[3] This article will review a practical approach to diagnosing EoE, including common scenarios where it can be picked up, as well as treatment and monitoring approaches.

Diagnosis of EoE

The most likely area that you will encounter EoE is during an emergent middle-of-the-night endoscopy for food impaction. If called in for this, EoE will be the cause in more than 50% of patients.[4] However, the diagnosis can be made only if esophageal biopsies are obtained at the time of the procedure. This is a critical time to decrease diagnostic delay, as half of patients are lost to follow-up after a food impaction.[5] Unfortunately, although taking biopsies during index food impaction is guideline-recommended, a quality metric, and safe to obtain after the food bolus is cleared, this is infrequently done in practice.[6,7]

The next most likely area for EoE detection is in the endoscopy suite where 15%-23% of patients with dysphagia and 5%-7% of patients undergoing upper endoscopy for any indication will have EoE.[4] Sometimes EoE will be detected "incidentally" during an open-access case (for example, in a patient with diarrhea undergoing evaluation for celiac). In these cases, it is important to perform a careful history (as noted below) as subtle EoE symptoms can frequently be identified. Finally, when patients are seen in clinic for solid food dysphagia, EoE is clearly on the differential. A few percent of patients with refractory heartburn or chest pain will have EoE causing the symptoms rather than reflux,[4] and all patients under consideration for antireflux surgery should have an endoscopy to assess for EoE.

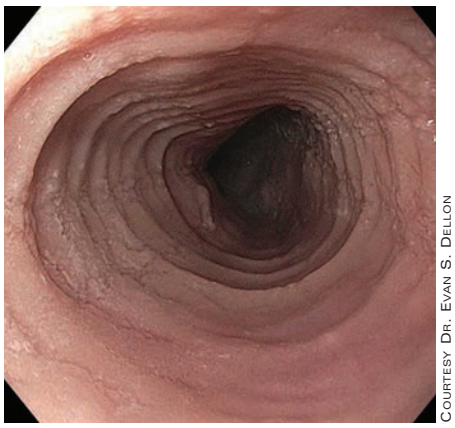
When talking to patients with known or suspected EoE, the history must go beyond general questions about dysphagia or trouble swallowing. Many patients with EoE have overtly or subconsciously modified their eating behaviors over many years to minimize symptoms, may have adapted to chronic dysphagia, and will answer "no" when asked if they have trouble swallowing. Instead, use the acronym "IMPACT" to delve deeper into possible symptoms.[8] Do they "**I**mbibe" fluids or liquids between each bite to help get food down? Do they "**M**odify" the way they eat (cut food into small bites; puree foods)? Do they "**P**rolong" mealtimes? Do they "**A**void" certain foods that stick? Do they "**C**hew' until their food is a mush to get it down? And do they "**T**urn away" tablets or pills? Pill dysphagia is often a subtle symptom, and sometimes the only symptom elicited.

Additionally, it may be important to ask a partner or family member (if present) about their observations. They may provide insight (eg, "yes — he chokes with every bite but never says it bothers him") that the patient might not otherwise provide. The suspicion for EoE should also be increased in patients with concomitant atopic diseases and in those with a family history of dysphagia or who have family members needing esophageal dilation. It is important to remember that EoE can be seen across all ages, sexes, and races/ethnicities.

Dr. Dellon is based at the Center for Esophageal Diseases and Swallowing, Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, Chapel Hill. He disclosed research funding, consultant fees, and educational grants from multiple companies.

Diagnosis of EoE is based on the AGREE consensus,[9] which is also echoed in the recently updated American College of Gastroenterology (ACG) guidelines.[10] Diagnosis requires three steps. First, symptoms of esophageal dysfunction must be present. This will most typically be dysphagia in adolescents and adults, but symptoms are nonspecific in children (eg, poor growth and feeding, abdominal pain, vomiting, regurgitation, heartburn).

Second, at least 15 eosinophils per high-power field (eos/hpf) are required on esophageal biopsy, which implies that an endoscopy be performed. A high-quality endoscopic exam in EoE is of the utmost importance. The approach has been described elsewhere,[11] but enough time on insertion should be taken to fully insufflate and examine the esophagus, including the areas of the gastroesophageal junction and upper esophageal sphincter where strictures can be missed, to gently wash debris, and to assess the endoscopic findings of EoE. Endoscopic findings should be reported using the validated EoE Endoscopy Reference Score (EREFS),[12] which grades five key features. EREFS is reproducible, is responsive to treatment, and is guideline-recommended (see photo).[6,10] The features are edema (present=1), rings (mild=1; moderate=2; severe=3), exudates (mild=1; severe=2), furrows (mild=1; severe=2), and stricture (present=1; also estimate diameter in mm) and are incorporated into many endoscopic reporting programs. Additionally, diffuse luminal narrowing and mucosal fragility ("crepe-paper" mucosa) should be assessed.



COURTESY DR. EVAN S. DELLON

Optimal view of the esophagus is shown in a patient newly diagnosed with EoE.

Eosinophilic esophagitis is a relatively newer disease entity, first reported only 30 years ago, and our diagnostic and therapeutic approaches have changed over the decades. Dr. Evan Dellon, leading expert in this field, describes his diagnostic approach, including a clear history beyond generic questions of dysphagia, endoscopic evaluation with biopsy, and ruling out other causes of esophageal eosinophilia.

Dellon emphasizes that treatment should target both inflammation and fibrostenosis and reviews the guidelines and evidence behind first-line treatments, surveillance, and long-term maintenance.

Judy Trieu, MD, MPH
Editor in Chief
The New Gastroenterologist

After this, biopsies should be obtained with at least six biopsy fragments from different locations in the esophagus. Any visible endoscopic abnormalities should be targeted (the highest yield is in exudates and furrows). The rationale is that EoE is patchy and at least six biopsies will maximize diagnostic yield.[10] Ideally the initial endoscopy for EoE should be done off of treatments (like proton pump inhibitors [PPIs] or diet restriction) as these could mask the diagnosis. If a patient with suspected EoE has an endoscopy while on PPI, and the endoscopy is normal, a diagnosis of EoE cannot be made. In this case, consideration should be given as to stopping the PPI, allowing a washout period (at least 1-2 months), and then repeating the endoscopy to confirm the diagnosis. This is important as EoE is a chronic condition necessitating life-long treatment and monitoring, so a definitive diagnosis is critical.

The third and final step in diagnosis is assessing for other conditions that could cause esophageal eosinophilia.[9] The most common differential diagnosis is gastroesophageal reflux disease (GERD). In some cases, EoE and GERD overlap or can have a complex relationship.[13] Unfortunately the location of the eosinophilia (ie, distal only) and the level of the eosinophil counts are not useful in making this distinction, so all clinical features (symptoms, presence of erosive esophagitis, or a hiatal hernia endoscopically), and ancillary reflex testing when indicated may be required prior to a formal EoE diagnosis. After the diagnosis is established, there should be direct communication with the patient to review the diagnosis and select treatments. While it is possible to convey results electronically in a messaging portal or with a letter, a more formal interaction, such as a clinic visit, is recommended because this is a new diagnosis of a chronic condition. Similarly, a new diagnosis of inflammatory bowel disease would never be made in a pathology follow-up letter alone.

Treatment of EoE

When it comes to treatment, the new guidelines emphasize several points.[10] First, there is the concept that anti-inflammatory treatment should be paired with assessment of fibrostenosis and esophageal dilation; to do either in isolation is incomplete treatment. It is safe to perform dilation both prior to anti-inflammatory treatment (for example, with a critical stricture in a patient with dysphagia) and after anti-inflammatory treatment has been prescribed (for example, during an endoscopy to assess treatment response).

Second, PPIs, swallowed topical corticosteroids (tCS), or dietary elimination are all acceptable first-line treatment options for EoE. A shared decision-making framework should be used for this discussion. If dietary elimination is selected,[14] based on new clinical trial data, guidelines recommend using empiric elimination and starting with a less restrictive diet (either a one-food elimination diet with dairy alone or a two-food elimination with dairy and wheat elimination). If PPIs are selected, the dose should be double the standard reflux dose. Data are mixed as to whether to use twice-daily dosing (ie, omeprazole 20 mg twice daily) or once-a-day dosing (ie, omeprazole 40 mg daily), but total dose and adherence may be more important than frequency.[10]

Goals of EoE treatment include improvement in symptoms, but also improvement in endoscopic and histologic features to prevent complications. Symptoms in EoE do not always correlate with underlying biologic disease activity.

For tCS use, either budesonide or fluticasone can be selected, but budesonide oral suspension is the only Food and Drug Administration (FDA)–approved tCS for EoE.[15] Initial treatment length is usually 6-8 weeks for diet elimination and 12 weeks for PPI and tCS. In general, it is best to pick a single treatment to start, and reserve combining therapies for patients who do not have a complete response to a single modality as there are few data to support combination therapy.

After initial treatment, it is critical to assess for treatment response.[16] Goals of EoE treatment include improvement in symptoms, but also improvement in endoscopic and histologic features to prevent complications. Symptoms in EoE do not always correlate with underlying biologic disease activity: Patients can minimize symptoms with careful eating; they may perceive no difference in symptoms despite histologic improvement if a stricture persists; and they may have minimal symptoms after esophageal dilation despite ongoing inflammation. Because of this, performing a follow-up endoscopy after initial treatment is guideline-recommended.[10,17] This allows assessing for endoscopic improvement, re-assessing for fibrostenosis and performing dilation if indicated, and obtaining esophageal biopsies. If there is nonresponse, options include switching between other first-line treatments or considering "stepping-up" to dupilumab which is also an FDA-approved option for EoE that is recommended in the guidelines.[10,18] In some cases where patients have multiple severe atopic conditions such as asthma or eczema that would warrant dupilumab use, or if patients are intolerant to PPIs or tCS, dupilumab could be considered as an earlier treatment for EoE.

Long-Term Maintenance

If a patient has a good response (for example, improved symptoms, improved endoscopic features, and <15 eos/hpf on biopsy), treatment can be maintained long-term. In almost all cases, if treatment is stopped, EoE disease activity recurs.[19] Patients could be seen back in clinic in 6-12 months, and then a discussion can be conducted about a follow-up endoscopy, with timing to be determined based on their individual disease features and severity.[17]

Patients with more severe strictures, however, may have to be seen in endoscopy for serial dilations. Continued follow-up is essential for optimal care. Just as patients can progress in their disease course with diagnostic delay, there are data that show they can also progress after diagnosis when there are gaps in care without regular follow-up.[20] Unlike other chronic esophageal disorders such as GERD and Barrett's esophagus and other chronic gastrointestinal inflammatory conditions like inflammatory bowel disease, however, EoE is not associated with an increased risk of esophageal cancer.[21,22]

Given its increasing frequency, EoE will be commonly encountered by gastroenterologists both new and established. Having a systematic approach for diagnosis, understanding how to elicit subtle symptoms, implementing a shared decision-making framework for treatment with a structured algorithm for assessing response, performing follow-up, maintaining treatment, and monitoring patients long-term will allow the large majority of EoE patients to be successfully managed. ■

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New AGA Update on Screening

Gastric Cancer Prevention *from page 1*

programs in gastroenterology at the University of Alabama at Birmingham.

Morgan, who wasn't involved with the AGA update, served as lead author for the ACG guideline and co-author of the ACG-ASGE quality indicators (QI). He also co-authored the 2024 ACG clinical guideline on treating *Helicobacter pylori* infection, which has implications for gastric cancer (2024 Sep. doi: 10.14309/ajg.0000000000002968).

"The AGA and ACG updates provide detail, while the QI document is an enforcer with medical, legal, and reimbursement implications," he said. "We have an alignment of the stars with this overdue move toward concrete surveillance for high-risk lesions in the stomach."

The clinical practice update was published in *Gastroenterology* (2025 Feb. doi: 10.1053/j.gastro.2024.11.001).

Gastric Cancer Screening

Gastric cancer remains a leading cause of preventable cancer and mortality in certain US populations, the authors wrote. The top ways to reduce mortality include primary prevention, particularly by eradicating *H pylori*, and secondary prevention through screening and surveillance.

High-risk groups in the United States should be considered for gastric cancer screening, including first-generation immigrants from high-incidence regions and potentially other non-White racial and ethnic groups, those with a family history of gastric cancer in a first-degree relative, and those with certain hereditary GI polyposis or hereditary cancer syndromes.

Endoscopy remains the best test for screening or surveillance of high-risk groups, the authors wrote, since it allows for direct visualization to endoscopically stage the mucosa, identify any concerning areas of neoplasia, and enable biopsies. Both endoscopic and histologic staging are key for risk stratification and surveillance decisions.

Dr. Morgan

In particular, clinicians should use a high-definition white-light endoscopy system with image enhancement, gastric mucosal cleansing, and insufflation to see the mucosa. As part of this technique, clinicians should allow for adequate visual inspection time, photodocumentation, and systematic biopsy protocol for mucosal staging, where appropriate.

Further, clinicians should consider *H pylori* eradication as an essential adjunct to endoscopic screening, the authors wrote. Opportunistic screening for *H pylori* should be considered in high-risk groups, and familial-based testing should be considered among adult household members of patients who test positive for *H pylori*.

Endoscopic Biopsy and Diagnosis

In patients with suspected gastric atrophy — with or without GIM — gastric biopsies should be obtained with a systematic approach, the authors wrote. Clinicians should take a minimum of five biopsies, sampling from the antrum/incisura and corpus.

"The AGA and ACG updates provide detail, while the QI document is an enforcer with medical, legal, and reimbursement implications."

Endoscopists should work with their pathologists on consistent documentation of histologic risk-stratification parameters when atrophic gastritis is diagnosed, the authors wrote. To inform clinical decision-making, documentation should include the presence or absence of *H pylori* infection, severity of atrophy or metaplasia, and histologic subtyping of GIM.

Although GIM and dysplasia are endoscopically detectable, these findings often go undiagnosed when endoscopists aren't familiar with the characteristic visual features, the authors wrote. More training is needed, especially in the United States, and although artificial intelligence tools appear promising for detecting early gastric neoplasia, data remain too preliminary to recommend routine use, the authors added.

Since indefinite and low-grade dysplasia can be difficult to identify by endoscopy and accurately diagnoses on histopathology, all dysplasia should be confirmed by an experienced gastrointestinal pathologist, the authors wrote. Clinicians should refer patients with visible or nonvisible dysplasia to an endoscopist or center with expertise in gastric neoplasia.

Endoscopic Management and Surveillance

If an index screening endoscopy doesn't identify atrophy, GIM, or neoplasia, ongoing screening should be based on a patient's risk factors and preferences. If the patient has a family history or multiple risk factors, ongoing screening should be considered. However, the optimal screening intervals in these scenarios aren't well-defined.

Patients with confirmed gastric atrophy should undergo risk stratification, the authors wrote. Those with severe atrophic gastritis or multifocal/incomplete GIM would likely benefit from endoscopic surveillance, particularly if they have other risk factors such as family history. Surveillance should be considered every 3 years, though shorter intervals may be advisable for those with multiple risk factors such as severe GIM.

Patients with high-grade dysplasia or early gastric cancer should undergo endoscopic submucosal dissection (ESD), with the goal of en bloc, R0 resection to enable accurate pathologic staging and the intent to cure. Eradicating active *H pylori* infection is essential — but shouldn't delay endoscopic intervention, the authors wrote.

In addition, patients with a history of successfully resected gastric dysplasia or cancer should undergo endoscopic surveillance. Although post-ESD surveillance intervals have been suggested in other recent AGA clinical practice updates, additional data are needed, particularly for US recommendations, the authors wrote.

Continued on following page

New Fecal Product to Aid Microbiome Research

BY DIANA SWIFT

The US National Institute of Standards and Technology (NIST) has developed precisely measured human fecal material to foster a new era in gut microbiome research.

According to AGA's Center for Gut Microbiome Research & Education, this critical resource will help advance the utility and reproducibility of microbiome-based diagnostics — "which still remain relatively meaningless clinically, although patients continue to buy direct-to-consumer tests, and a standard reference material will mean there's a better way to ensure quality control and accuracy."

Though not a therapeutic, Human Fecal Material RM is expected to speed up gastrointestinal (GI) therapeutics since many microbiome-based drugs are inspired by fecal transplants with human stool as the developmental starting point. A standardized reference material will be an important resource as industry develops and tests new drugs. It can be purchased online at the NIST Store (shop.nist.gov).

The product consists of eight frozen vials of exhaustively studied human feces suspended in aqueous solution. Available are more than 25 pages of data identifying the key microbes and biomolecules in the material (see Reference Material 8048: https://tsapps.nist.gov/srmext/certificates/8048.pdf). Scientists, including those working at biopharmaceutical and biotech companies, can use this material to further their research and develop new drugs that target the microbiome, including treatments that contain living bacteria.

Development

According to NIST, the stool material is "the most precisely measured, scientifically analyzed, and richly characterized human fecal standard ever produced.

Dr. Jackson

"The project ran for about 6 years from start to finish, the last 2 for manufacturing, characterization, and writing," said NIST molecular geneticist Scott A. Jackson, PhD, who helped develop the product. "We hope our reference material will lay the foundation for gut microbiome research to thrive and reach its full potential."

As founder of NIST's Complex Microbial Systems Group, Jackson is leading international efforts to improve microbiome and metagenomic measurements by organizing inter-lab studies and refining reference materials and methods.

The project collected stool from two cohorts of donors, ie, vegetarians and omnivores, with each cohort comprising four to six donors. Material from each cohort was pooled and homogenized before being aliquoted into 5000 vials per cohort. About 300 tubes from each cohort were picked, and aliquots then underwent multiomic analyses.

Offering his perspective on the new product, Sudhir K. Dutta, MBBS, associate professor in the division of gastroenterology and hepatology at Johns Hopkins University School of Medicine, Baltimore, said, "This tool will be 100% useful for microbiome research."

Dr. Holtz

And according to Lori Holtz, MD, MSPH, professor of pediatric gastroenterology, hepatology, and nutrition at Washington University School of Medicine in St. Louis, Missouri, the material will aid microbiome research by allowing interpretability and repeatability across studies. "Microbiome research is a relatively new field, and protocols differ from group to group and lab to lab, so it's been difficult to compare results across studies," she told *GI & Hepatology News*. "A standard stool product will allow for greater comparability in preclinical studies and later clinical trials testing interventions to alter the microbiome."

The NIST developers are looking forward to reaction from the GI research community. "Over the last several years, we've released smaller pilot batches of material to smaller groups of stakeholders," said Jackson. "We've used the feedback on these earlier batches to inform the manufacturing and characterization of the final batch that was released in March, but we don't have any feedback yet on the current material."

"A standard stool product will allow for greater comparability in preclinical studies and later clinical trials testing interventions to alter the microbiome."

Jackson, Dutta, and Holtz disclosed having no relevant competing interests. ■

Continued from previous page

Although type 1 gastric carcinoids in patients with atrophic gastritis are typically indolent, especially if less than 1 cm, endoscopists may consider resecting them and should resect lesions between 1 and 2 cm. Patients with lesions over 2 cm should undergo cross-sectional imaging and be referred for surgical resection, given the risk for metastasis.

Dr. El-Serag

Patient-Centered Approach

The guideline authors suggested thinking about screening and surveillance on a patient-level basis. For instance, only those who are fit for endoscopic or potentially surgical treatment should be screened for gastric cancer and continued surveillance of GPMC, they wrote. If a person is no longer fit for endoscopic or surgical treatment, whether because of life expectancy or other comorbidities, then screening should be stopped.

"Recent changes in the epidemiology and endoscopic management of gastric polyps makes this update timely and important."

In addition, to achieve health equity, clinicians should take a personalized approach to assess a patient's risk for gastric cancer and determine whether to pursue screening and surveillance, the authors wrote. Modifiable risk factors — such as tobacco use, high-salt and processed food diets, and lack of health care — should also be addressed, since most of these risk factors disproportionately affect high-risk patients and represent health care disparities, they added.

"This update provides clinicians with a framework for understanding the natural history and epidemiology of gastric polyps, as well as guidance on best practices for the endoscopic detection and classification of gastric polyps, best practices for the endoscopic resection of gastric polyps, and best practices for endoscopic surveillance following resection," said Hashem El-Serag, MD, professor and chair of medicine at the Baylor College of Medicine and director of the Texas Medical Center Digestive Diseases Center in Houston.

El-Serag, who wasn't involved with the clinical practice update, has researched and published on consensus around the diagnosis and management of GIM.

"Stomach polyps are commonly found during routine endoscopic procedures. They are mostly asymptomatic and incidental, and therefore, clinicians may not be prepared ahead of time on how to deal with them," he said. "The appropriate management requires proper identification and sampling of the polyp features and the uninvolved gastric mucosa, as well as a clear understanding of the risk factors and prognosis. Recent changes in the epidemiology and endoscopic management of gastric polyps makes this update timely and important."

The update received no particular funding. The authors disclosed receiving grant support, having consultant relationships with, and serving in advisory roles for numerous pharmaceutical, biomedical, and biotechnology firms. Morgan and El-Serag reported having no relevant disclosures. ■