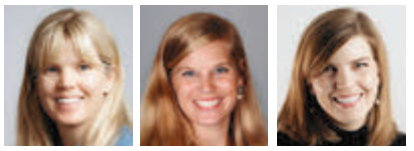

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GI&Hepatology News

January 2025

Volume 19 / Number 1

FERNANDA CARRASCO | DREAMSTIME.COM

'Watershed Moment' Semaglutide Shown to Be Effective in MASH

BY CAROLYN CRIST

FROM AASLD 24

SAN DIEGO — Semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, appears to safely and effectively treat metabolic dysfunction–associated steatohepatitis (MASH) among patients with moderate to advanced liver fibrosis, according to interim results from a phase 3 trial.

At 72 weeks, a 2.4-mg once-weekly subcutaneous dose of semaglutide demonstrated superiority, compared with placebo, for the two primary endpoints: resolution of steatohepatitis with no worsening of fibrosis and improvement in liver fibrosis with no worsening of steatohepatitis.

"It's been a long journey. I've been working with GLP-1s for 16 years, and it's great to be able to report the first GLP-1 receptor agonist to demonstrate efficacy in a phase 3 trial for MASH," said lead author Philip Newsome, MD, PhD, director of the Roger Williams Institute of Liver Studies at King's College London in England.

"There were also improvements in a slew of other noninvasive markers," said Newsome, who presented the findings at The Liver Meeting 2024: American Association for

See **Semaglutide** · *page 11*

AGA Guidelines Endorse Earlier Use of High-Efficacy Drugs for Ulcerative Colitis

BY DIANA SWIFT

FROM GASTROENTEROLOGY

In a rapidly expanding therapeutic landscape, the American Gastroenterological Association (AGA) has issued updated practice guidelines for the pharmacological management of moderate to severe ulcerative colitis (UC) in adult outpatients.

"These are the first living guidelines published by a GI society, highlighting the interest and need to provide timely guidance to all stakeholders in a rapidly evolving field," first author Siddharth Singh, MD, of the Division of Gastroenterology in the Department of Medicine at University of California, San Diego, said in an interview. Living guidance allows for ongoing revision of individual recommendations as new data emerge. Nearly 2 million Americans have UC (Gastroenterology. 2023 Nov;165[5]:1197.e2-1205.e2).

Issued in *Gastroenterology* (2024 Dec. doi: 10.1053/j.gastro.2024.10.001) and updating the last guidance in 2020 (Gastroenterology. 2020 Apr;158[5]:1450-1461), the recommendations suggest more efficacious drugs should be used sooner. When used early, "advanced therapies including biologics and small-molecule drugs are more effective than 5-aminosalicylates [5-ASAs] or thiopurines and methotrexate for most patients with moderate to severe UC and those with poor prognostic factors,"

See **Guidelines** · *page 23*

GI & HEPATOLOGY NEWS
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LETTER FROM THE EDITOR

An Exciting Time to Be a Gastroenterologist


Dr. Adams

New inflammatory bowel disease (IBD) pharmacotherapeutics have been developed at a dizzying pace — our IBD patients have so many more treatment options today than they did just a decade ago, making treatment decisions much more complex.

Happy New Year, everyone! As we enter 2025, I've been reflecting on just how much has changed in the field of gastroenterology since I completed my fellowship a decade ago.

After developing and disseminating highly effective treatments for hepatitis C, the field of hepatology has shifted rapidly toward identifying and managing other significant causes of liver disease, particularly alcohol-associated liver disease and metabolic dysfunction–associated steatotic liver disease (MASLD). New disease nomenclatures have been developed that have changed the way we describe common diseases — most notably, NALFD is now MASLD and FGID are now DGBI.

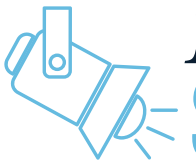
There have been marked advances in obesity management, including not only innovations in endobariatric therapies such as intragastric balloons and endoscopic sleeve gastroplasty, but also the introduction of glucagon-like peptide 1 (GLP-1) agonists, which offer new hope in effectively tackling the obesity epidemic. Our growing understanding of the microbiome's role in health has opened new avenues for treating GI diseases and introduced the potential for more personalized treatment approaches based on individual microbiome profiles. New inflammatory bowel disease (IBD) pharmacotherapeutics have been developed at a dizzying pace — our IBD patients have so many more treatment options today than they did just a decade ago, making treatment decisions much more complex.

Finally, we are just beginning to unleash the potential of artificial intelligence, which is likely to transform the field of medicine and GI clinical practice over the next decade. To be sure, it is an exciting time to be a gastroenterologist, and I can't wait to see to what the next decade of innovation and discovery will bring.

In this month's issue of *GI & Hepatology News*, we highlight the first-ever "living" AGA clinical practice guideline on pharmacologic management of moderate to severe ulcerative colitis. From the recent AASLD meeting, we bring you exciting new data demonstrating the effectiveness of GLP-1 agonists (specifically, semaglutide) in treating MASH. In January's Member Spotlight column, we introduce you to Drs. Mindy, Amy, and Kristen Engevik, who share their fascinating career journeys as GI researchers (and sisters!). In our quarterly Perspectives column, Dr. Brijesh Patel and Dr. Juan Gomez Cifuentes share their experiences counseling patients regarding lifestyle modifications for gastroesophageal reflux disease and what strategies have proved to be the most effective adjuncts to pharmacotherapy. We hope you enjoy this and all the exciting content in our January issue. ■

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

Call for Nominations



Member SPOTLIGHT

Nominate your colleagues to be featured in a Member Spotlight. Email GINews@gastro.org.

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GI&Hepatology News

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Member SPOTLIGHT

Three Sisters Embrace 'Collaborative Spirit' of GI Science

BY JENNIFER LUBELL
MDedge News


Dr. Amy Engevik


Dr. Mindy Engevik


Dr. Kristen Engevik

They all share the same genes—and job title.

Amy Engevik, PhD, Mindy Engevik, PhD, and most recently, Kristen Engevik, PhD, work as assistant professors in the Department of Regenerative Medicine and Cell Biology at the Medical University of South Carolina (MUSC) in Charleston. Each has her own lab, working in different specialties. But if one sister needs the others, it's reassuring to know they're not far away.

"We have very different points of view. I'm interested in microbes. Amy's really interested in myosin-mediated trafficking, and Kristen's interested in viruses and purinergic signaling. It's awesome that we can all work in the same field but have very different questions. And there's so many questions that we can tackle," said Mindy Engevik, the oldest of the trio.

If Mindy's students need help with staining, she sends them to Amy's lab. If they need help with calcium signaling and live cell imaging, she'll send them to Kristen's lab. "We interchange our expertise a lot," said Mindy.

It's nice to have a sister down the hall at work who can advise you on RNA-sequencing analysis or immunofluorescence imaging, noted Amy Engevik. "You can ask them: 'Can you just walk my student through this for a minute?' Or, could they help with organoid cultures you don't have time for right now?"

Kristen, who joined her older sisters at MUSC in 2024, observed that "having a little bit of the variety with our backgrounds and training really helps bring out the collaborative spirit of science."

In an interview, the Engevik sisters spoke more about their familial network, their shared love of gastroenterology (GI) science, and how they've parlayed their expertise into other critical areas of research.

Growing up, did you ever think that you would choose similar career paths? How did you all become interested in GI research?

Mindy Engevik: As kids we were all interested in nature and the world around us. We all liked being outside. Amy and I were obsessed with rocks and classifying plants and rocks. We all had a general interest in science. But I personally didn't think that all three of us would go into the same thing and that we'd be working together as adults.

Amy Engevik: Once we got into high school and college, we all became very close and we all majored in biology. That set the stage for our interest in science and our love of science. Then, we all kind of fell in love with the GI tract and chose postdocs that were GI focused. Since Mindy and I graduated a year apart, ultimately our goal was to form a lab and work together.

Kristen Engevik: I was interested in science when my sisters were both at college studying for biology and talking about the things they were learning in microbiology and physiology. But I don't think until I joined the PhD program that I was ever like: "Oh yeah, we're all going to be in science, and it's all going to be one big giant collaborative multi-lab collaboration."

What do each of you love about the field of gastroenterology?

Mindy Engevik: At our heart, we're all people that love problem-solving. A fun fact about us is on Thursdays once a month, we do a puzzle competition here in Charleston. We're really into it. But I think we genuinely like the problem-solving nature of the GI tract, and there's so many diverse questions that you can answer.

Amy Engevik: I love that the scientific community in the GI community is so wonderful. They are very kind, helpful people. Some other fields are more competitive and more cutthroat. I feel like I have such a great network of people to reach out to if I have problems or questions. And I think other fields don't have such a wonderful welcoming community that is very inclusive and dynamic.

Kristen Engevik: The nice thing with studying the GI tract is all things essentially lead to the gut. You can collaborate with other scientists and go into the gut-brain axis, or there's the cardiovascular-gut axis and all these different places that you can also go, or different diseases that don't necessarily seem to originate at the gut but have a lot of effects on the gut. There's a lot of variation that we can do within GI.

Each of you has focused on a different area of digestive disease. Can each of you briefly discuss your areas of study and any findings or discoveries you'd like to highlight?

Mindy Engevik: My research focuses on microbial-host interactions. We're really interested in how microbes colonize the gastrointestinal tract, how they interact with mucus — which I think is an important aspect of the gut that sometimes is overlooked — and how their metabolites really impact host health. One thing that I'm particularly proud of is we've really been starting to understand the neurotransmitters that bacteria generate and how they influence specific cells within the gut. It's an exciting time to be doing both microbiology and gut physiology.

Amy Engevik: I study the host side of things; the gastric or the GI epithelium, and how a specific molecular motor contributes to trafficking in the GI tract. Recently, I've been going back to some of my PhD work in the stomach. In a high-fat diet model, we're finding that there are early metaplastic changes in the stomach. I think the stomach is very often overlooked within the GI tract. And I think it really sets the stage for the lower GI tract for the microbiome that colonizes the colon and the small intestine. I think that changes in the stomach really should come to the forefront of GI. Those changes have profound impacts on things like colorectal cancer and inflammatory bowel disease.

Kristen Engevik: I'm also more on the epithelial side with Amy. My new lab's work is going to be focusing on understanding cell communications, specifically through extracellular purines, which is known as purinergic signaling, and understanding what the effects are during both homeostasis and disease, since it hasn't been studied within the gut itself. From my work in postdoctoral training, we found that this communication is important for a lot of aspects, specifically during viral infection. But I have some preliminary data that shows it may also have an important role during disease, like colitis. My lab is interested in understanding what this epithelial communication is and are there ways to increase or decrease the signaling depending on the disease?

You're all skilled in analyzing bioinformatics data. How do you apply this skill in your GI research?

Mindy Engevik: We all got our PhDs in systems biology and physiology, so we were forced to take computational analysis classes. I remember at the time thinking, "Oh, I'm probably not going to use a bunch of this." And then it really captured our attention. We realized how valuable it was and how much information you could glean.

We do a lot of work using publicly available data sets. I think there's a wealth of information out there now with single-cell sequencing data and bulk RNA-sequencing data of different sites in the GI tract. It's been a very valuable time to data mine and look especially at inflammatory

Continued on following page

Continued from previous page

bowel disease and colorectal cancer. We've been really focused on all our favorite genes of interest. I've been looking at a lot of the mucins and IBD [inflammatory bowel disease] and cancer. Amy's been looking at Myosin-Vb and other myosin and binding partners like Rabs, and Kristen has been looking at purinergic signaling receptors.

All three of you recently worked together to identify a possible genetic driver of uterine corpus endometrial cancer, the fourth deadliest cancer in women. Where are you in the research process right now?

Mindy Engevik: Our mom was diagnosed with cancer, so we took quite a bit of time off to go to California to help her with her chemotherapy, surgery, and radiation. While we were there, we decided to do some computational analyses of cancers that affect women as our way to deal with this devastating disease. We were really fascinated to find that Myosin-Vb, which is Amy's favorite gene of interest, was highly up-regulated in tumors from uterine and corpus endometrial cancer.

This was independent of the age of the patient, the stage of the cancer, the grade of the tumors. We figured out that the promoter region of the gene was hypomethylated, so it was having a higher expression. And that led to changes in metabolism and it linked very closely with what we were seeing in the gut, what Myosin-Vb was doing. We have some uterine cancer tumor cells in the lab that we've been growing and we're going to really prove that it's Myosin-Vb that's driving some of these metabolism phenotypes. And the nice thing is at least there is a Myosin-Vb inhibitor available.

We also have a paper under review, identifying what Myosin-Vb is doing in cancer in the colon. So we're excited to continue both the uterine cancer part but then also the colorectal cancer part using our same processes.

Amy Engevik: We're going to be generating a mouse model that I think will be helpful since it's in vivo. Sometimes things in vivo behave very differently than they do in vitro, so I think it'll be a nice coupling of in vitro data with in vivo, taking that computational base and expanding it into more mechanistic studies and more experimental approaches where we can actually develop uterine cancer in the mice and then see if we can knock out Myosin-Vb specifically in that tissue and prevent it from either happening in the first place or decrease its pathogenesis.

Courtesy Dr. Mindy Engevik

Drs. Kristen, Amy, and Mindy Engevik (from L to R) often vacation together when they leave their labs.

What challenges have you faced in your career? How do you offer each other support?

Mindy Engevik: I think for any female scientists trying to have an independent career, there are some hurdles. An article in *Nature* recently stated that women receive less credit than their male counterparts and another article in *Science* demonstrated that women who are last authors on publications are cited less. That's something that all women must deal with everywhere. I think it's been incredibly helpful for us since there's three of us. I think it gives us extra visibility in the field.

Amy Engevik: There's a lot of microaggressions and things that can hinder your career success. I think that we've definitely had that. And I think the academic landscape is changing a little bit now that more women are becoming principal investigators and then rising through the ranks of academia. So I think there's a lot of hope for the future women, but I think it's still quite challenging.

Kristen Engevik: Things do seem to be getting better as there are more women as faculty members in certain departments. Science is getting better as things progress. However, there are still a lot of difficulties in trying to get credit for what you do, and getting the promotions.

Mindy Engevik: We have a built-in sisterhood, if you will. So I'm always going to champion Amy or Kristen. If there's an award that I can nominate them for, I'm always going to do it. If there's something that I think they should apply for that maybe they hadn't seen, I'm going to make sure I put it on the radar. I think that's just incredibly helpful, having people that have your best interest in mind.

Every project we have is basically a big collaboration. We have a lot of papers from our postdocs where we are coauthors. Now, as principal investigators, we have a lot of papers together. And I think in the future you'll be seeing a lot of coauthored publications from our group as well. ■

Lightning round

Texting or talking?
KE: Talking

Favorite city in US besides the one you live in?
AE: Boston

Favorite breakfast?
ME: Biscuits and grits

Place you most want to travel?
KE: Antarctica

Favorite junk food?
AE: French fries

Favorite season?
ME: Fall

Favorite ice cream flavor?
KE: Black raspberry chip

Number of cups of coffee you drink per day?
AE: None, I like Diet Coke

Song you have to sing along with when you hear it?
KE: Mamma Mia

Career pick if you weren't a gastroenterologist?
KE: National Park ranger

Best Halloween costume you ever wore?
AE: Princess Leia

Last movie you watched?
ME: Inside Out 2

Favorite type of music?
ME: ABBA

Favorite movie genre?
KE: Romantic comedies

Cat person or dog person?
AE: Neither, I like rabbits

Favorite sport?
ME: Surfing

Introvert or extrovert?
AE: Introvert

Favorite holiday?
ME: Halloween

➤ FROM THE AGA JOURNALS

Digestive Disease Mortality Higher for US Indigenous Communities

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Persistent racial, ethnic, and geographic disparities in digestive disease mortality rates across the United States disproportionately impact American Indian and Alaska Native communities, which experience the highest death rates and ongoing increases, according to a recent study.

Policymakers, healthcare providers, and communities need to respond with targeted interventions and collaborative efforts that address these inequities and advance digestive health equity, lead author Wafa A. Aldhaleei, MD, of Mayo Clinic, Rochester, Minnesota, and colleagues reported.

"Several studies have reported the epidemiological characteristics of certain digestive diseases such as pancreatitis, liver and biliary diseases, and inflammatory bowel disease," the investigators wrote in *Clinical Gastroenterology and Hepatology* (2024 Aug. doi: 10.1016/j.cgh.2024.07.035). "These studies provide insights into the US burden by sex and racial and ethnic disparities of various digestive diseases individually. However, little is known about racial disparities in the United States digestive diseases mortality burden."

Continued on following page

Human Milk Boosts Intestinal Growth, Immune Health of Fetal Organoids

BY WILL PASS
MDedge News

FROM GASTRO HEP ADVANCES

Human milk enhances the growth, differentiation, and immune regulation of fetal intestinal organoids, compared with formula, according to investigators.

These findings suggest an important role for human milk in supporting intestinal health, and may inform strategies for reducing the risk of necrotizing enterocolitis (NEC) in preterm infants, lead author Lauren Smith, MD, of Yale School of Medicine, New Haven, Connecticut, and colleagues, reported.

"Compelling evidence has revealed that the largest risk factor for NEC apart from prematurity is formula feeding, while conversely, parental milk (PM) confers protection, with a 6- to 10-fold lower incidence of NEC among PM-fed infants compared to formula," the investigators wrote in *Gastro Hep Advances* (2024 Jul. doi: 10.1016/j.gastha.2024.07.007). "It is unknown whether this is due to the many known protective factors in PM or as a result of an injurious component present in formula or a combination of both."

To learn more, the investigators studied organoids cultured in a three-dimensional matrix and exposed to one of four dietary conditions: PM, donor human milk (DHM), standard formula (SF), or extensively hydrolyzed formula (HF). Organoids were grown in growth media supplemented with these diets for 5 days, followed by differentiation media for an additional 5 days. Growth, differentiation, and immune-related factors were analyzed using advanced imaging, RNA sequencing, and cytokine profiling.

The results demonstrated that human milk–fed organoids significantly outperformed formula-fed organoids in several measures. By the fifth day of growth media exposure, organoids supplemented with PM or DHM were larger and exhibited higher rates of proliferation, as evidenced by Ki67 staining. Organoids exposed to SF were the smallest and had the lowest proliferation and highest levels of apoptosis, while HF-fed organoids showed intermediate growth performance.

During the differentiation phase, organoids exposed to human milk developed more complex structures, forming buds with greater length and diameter compared to formula-fed organoids. PM was particularly effective, though DHM also promoted substantial differentiation. RNA sequencing revealed that organoids cultured with human milk upregulated genes involved in fatty acid metabolism and Wnt signaling, which are critical for cellular energy production and epithelial proliferation. In contrast, formula-fed organoids exhibited downregulation of cell cycle–promoting genes and showed an inflammatory gene signature.

Cytokine profiling further underscored the benefits of human milk. Organoids exposed to PM and DHM secreted higher levels of immune-regulating cytokines, such as thymic stromal lymphopoietin and macrophage colony-stimulating factor. In contrast, formula-fed organoids produced lower levels of these beneficial cytokines and higher levels of pro-inflammatory markers, including interleukin-18.

These findings suggest that human milk supports intestinal growth, differentiation, and immune regulation in ways that formula does not, and the investigators emphasized the importance of identifying specific bioactive factors in human milk.

"If the factors responsible for this effect can be identified, there could be significant clinical value in supplementing these components in DHM and formula to help prevent NEC and foster normal intestinal development in preterm infants," they concluded.

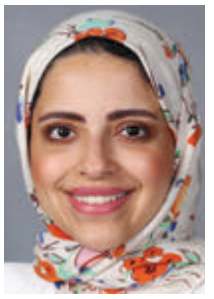
Future research will aim to isolate and supplement key components of human milk to enhance the nutritional and protective value of donor milk and formula. In addition, the investigators noted the need to explore potential sex-based differences in intestinal development, as the current study used only male-derived samples.

The research was supported by the Yale School of Medicine Medical Student Research Fellowship. The investigators disclosed no conflicts of interest. ■

Continued from previous page

As part of the Global Burden of Disease Study, the investigators analyzed data from the Institute of Health Metrics and Evaluation Global Health Data Exchange, including age-standardized digestive disease mortality rates for five racial and ethnic groups (Black, White, American Indian and Alaska Native, Asian and Pacific Islander, and Latino) between 2000 and 2019, with further subgroups based on sex, state, and county. Joinpoint regression analysis was employed to determine overall temporal trends by demography.

Results showed striking mortality rate differences across racial and ethnic groups. In 2019, digestive disease mortality rates were highest among American Indian and Alaska Native individuals, reaching 86.2 per 100,000 — over twice the rate seen in White (35.5 per 100,000), Black (33.6 per 100,000), and Latino (33.6 per 100,000) populations, and more than five times higher than in Asian and Pacific Islander individuals (15.6 per 100,000). Over the study period, American Indian and Alaska Native individuals experienced a significant 0.87% average annual increase in mortality rates, while White individuals saw a smaller increase of 0.12% annually. In contrast, Latino, Black, and Asian and Pacific Islander individuals had declining average annual rates.



Dr. Aldhaleei

'Our study reveals persistent racial, ethnic, and geographic disparities in digestive diseases mortality in the United States. Targeted interventions and further research are needed to address these disparities and promote digestive health equity.'

Geographic disparities in digestive disease mortality were significant, with West Virginia recording the highest state-level rate in 2019 at 44.8 deaths per 100,000, well above the national rate of 34.5 per 100,000. Certain regions with high concentrations of American Indian and Alaska Native populations, such as the Southwest Tribes service area (including Arizona and New Mexico) and the Plain Indians service area (spanning Montana, North Dakota, and South Dakota), reported mortality rates exceeding 70 per 100,000, more than double the national average. In Alaska, the American Indian and Alaska Native population's mortality rate surged with annual increases of up to 3.53% during some periods.

Analyses also revealed some notable sex-based trends. Among American Indian and Alaska Native individuals, males experienced a mortality rate increase of 0.87% annually, reaching 93.5 per 100,000 by 2019, while females saw an even sharper rise at 1.11% per year, with a mortality rate of 79.6 per 100,000 in 2019. For White individuals, the average annual percentage increase was 0.12% for males, bringing their rate to 40.2 per 100,000, and 0.30% for females, with a rate of 31.0 per 100,000 in 2019.

"Our study reveals persistent racial, ethnic, and geographic disparities in digestive diseases mortality in the United States," the investigators concluded. "Targeted interventions and further research are needed to address these disparities and promote digestive health equity. Collaboration among researchers, policymakers, healthcare providers, and communities is essential to achieve this goal."

This research was conducted as part of Global Burden of Disease, Injuries and Risk Factors Study, coordinated by the Institute of Health Metrics and Evaluation. The investigators disclosed no conflicts of interest. ■

Biomarkers Predict Villous Atrophy in Potential Celiac Disease Patients

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

In children with asymptomatic potential celiac disease (PCD), a panel of seven serum proteomic biomarkers can predict which individuals will go on to develop villous atrophy (VA), according to investigators.

Given that PCD patients present with positive serology and intact duodenal architecture, these findings may provide a much-needed tool for identifying patients who are more likely to benefit from early dietary interventions, lead author Renata Auricchio, MD, PhD, of the University of Naples Federico II, Italy, and colleagues reported.

"PCD offers the unique opportunity to observe the progression of gluten-induced tissue damage in celiac disease," the investigators wrote in *Gastroenterology* (2024 Sep. doi: 10.1053/j.gastro.2024.09.001). "These patients recognize gluten and produce specific autoantibodies, but have not developed intestinal damage."

The study included 31 children with asymptomatic PCD who were eating a gluten-containing diet. Serum samples from each child were analyzed for the relative abundance of 92 inflammation-linked proteins using a proximity extension immunoassay. Statistical analyses, including partial least-squares discriminant and linear discriminant analyses, were then applied to

Continued on following page

Patients with positive celiac serologies but normal villous architecture on biopsy are considered to have potential celiac disease (PCD). While the prevalence of PCD is not well-established, it is estimated to be around 1%. This study by Auricchio and colleagues investigates seven serum proteomic biomarkers that could help predict whether asymptomatic patients with PCD are at risk of developing villous atrophy (VA).


Dr. Moleski

The study also identifies specific inflammatory proteins present in PCD patients who are likely to develop VA. These biomarkers provide valuable insights into the pathogenesis of celiac disease and the development of VA in genetically predisposed individuals.

As celiac disease is increasingly diagnosed without biopsies, serum proteomic biomarkers could be crucial in identifying patients who may benefit from starting a gluten-free diet (GFD) earlier, potentially preventing complications. According to the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines, children can be diagnosed with celiac disease if their tissue transglutaminase immunoglobulin A level is 10 times the upper limit of normal, confirmed by a positive endomysial antibody test. However, this approach may lead to many patients committing to a lifelong GFD despite having only PCD, as biopsies may not have been performed. In this study, 60% of patients with PCD did not progress to VA, suggesting that biomarkers could help prevent unnecessary long-term GFD commitments.

Stephanie M. Moleski, MD, is the director of the Jefferson Celiac Center and associate professor in the division of gastroenterology at Thomas Jefferson University Hospital, Philadelphia. She reported no conflicts of interest.

‘Highlight’ of AASLD

Semaglutide *from page 1*

the Study of Liver Diseases (AASLD).

Although already seen in a broader context, “it’s nice to see a demonstration of the cardiometabolic benefits in the context of MASH and a reassuring safety profile,” he added.

Interim ESSENCE Trial Analysis

ESSENCE (NCT04822181) is an ongoing multicenter, phase 3 randomized, double-blind, placebo-controlled outcome trial studying semaglutide for the potential treatment of MASH.

Dr. Loomba

Dr. Chalasani

The trial includes 1200 participants with biopsy-defined MASH and fibrosis, stages F2 and F3, who were randomized 2:1 to a once-weekly subcutaneous injection of 2.4 mg of semaglutide or placebo for 240 weeks. After initiation, the semaglutide dosage was increased every 4 weeks up to 16 weeks when the full dose (2.4 mg) was reached.

In a planned interim analysis, the trial investigators evaluated the primary endpoints at week 72 for the first 800 participants, with biopsies taken at weeks 1 and 72.

A total of 534 people were randomized to the semaglutide group, including 169 with F2 fibrosis and 365 with F3 fibrosis. Among the 266 participants randomized to placebo, 81 had F2 fibrosis and 185 had F3 fibrosis.

At baseline, the patient characteristics were similar between the groups (mean age, 56 years; body mass index, 34.6). A majority of participants also were White (67.5%) and women (57.1%), and had type 2 diabetes (55.9%), F3 fibrosis (68.8%), and enhanced liver fibrosis (ELF) scores around 10 (55.5%).

For the first primary endpoint, 62.9% of those in the semaglutide group and 34.1% of those in the placebo group reached resolution of steatohepatitis with no worsening of fibrosis. This represented an estimated difference in responder proportions (EDP) of 28.9%.

In addition, 37% of those in the semaglutide group and 22.5% of those in the placebo group met the second primary endpoint of improvement in liver fibrosis with no worsening of steatohepatitis (EDP, 14.4%).

Among the secondary endpoints, combined resolution of steatohepatitis with a one-stage improvement in liver fibrosis occurred in 32.8% of the semaglutide group and 16.2% of the placebo group (EDP, 16.6%).

In additional analyses, Newsome and colleagues found 20%-40% improvements in liver enzymes and noninvasive fibrosis markers, such as ELF and vibration-controlled transient elastography liver stiffness.

Weight loss was also significant, with a 10.5% reduction in the semaglutide group compared with a 2% reduction in the placebo group.

Cardiometabolic risk factors improved as well, with changes in blood pressure measurements, hemoglobin A1c scores, and cholesterol values.

Although not considered statistically significant, patients in the semaglutide group also reported greater reductions in body pain.

In a safety analysis of 1195 participants at 96 weeks, adverse events, severe adverse events, and discontinuations were similar in both groups. Not surprisingly, gastrointestinal side effects were more commonly reported in the semaglutide group, Newsome said.

Highly Anticipated Results

After Newsome’s presentation, attendees applauded.

Rohit Loomba, MD, a gastroenterologist at the University of California, San Diego, who was not involved with the study, called the results the “highlight of the meeting.”

This sentiment was echoed by Naga Chalasani, MD, AGAF, a gastroenterologist at Indiana University Medical Center, Indianapolis, who called the results a “watershed moment in the MASH field” with “terrific data.”

Based on questions after the presentation, Newsome indicated that future ESSENCE reports would look at certain aspects of the results, such as the 10% weight loss among those in the semaglutide group, as well as the mechanisms of histological and fibrosis improvement.

“We know from other GLP-1 trials that more weight loss occurs in those who don’t have type 2 diabetes, and we’re still running those analyses,” he said. “Weight loss is clearly a major contributor to MASH improvement, but there seem to be some weight-independent effects here, which are likely linked to insulin sensitivity or inflammation. We look forward to presenting those analyses in due course.”

Dr. Brown

In a comment, Kimberly Ann Brown, MD, AGAF, chief of gastroenterology and hepatology at Henry Ford Health System in Detroit, Michigan, AASLD Foundation chair, and comoderator of the late-breaking abstract session, spoke about the highly anticipated presentation.

“This study was really the pinnacle of this meeting. We’ve all been waiting for this data, in large part because many of our patients are already using these medications,” Brown said. “Seeing the benefit for the liver, as well as lipids and other cardiovascular measures, is so important. Having this confirmatory study will hopefully lead to the availability of the medication for this indication among our patients.”

Newsome reported numerous disclosures, including consultant relationships with pharmaceutical companies, such as Novo Nordisk, Boehringer Ingelheim, and Madrigal Pharmaceuticals. Loomba has research grant relationships with numerous companies, including Hanmi, Gilead, Galmed Pharmaceuticals, Galectin Therapeutics, Eli Lilly, Bristol-Myers Squibb, and Boehringer Ingelheim. Chalasani has consultant relationships with Ipsen, Pfizer, Merck, Altimmune, GSK, Madrigal Pharmaceuticals, and Zydus. Brown reported no relevant disclosures. ■

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identify which proteins were associated with the development of VA.

After a mean follow-up period of 5.85 years, 14 participants developed VA (ie, celiac disease), while the remaining 17 remained asymptomatic.

Panel analysis revealed that specific inflammatory proteins, including interleukin (IL)–20, IL-2, sirtuin 2 (SIRT2), leukemia inhibitory factor (LIF), IL-22 receptor subunit a1, cystatin D (CST5), IL-17 receptor A, IL-15 receptor subunit a (RA), CUB domain–containing protein 1 (CDCP1), and IL-14, were 1.23- to 1.76-fold higher in children who developed VA. Among these, seven proteins — CDCP1, IL-2, LIF, IL10RA, SIRT2, CST5, and IL-4 — were able to significantly distinguish between symptomatic and asymptomatic cases in a linear discriminant model. This panel of seven proteins achieved a predictive accuracy of 96.8% in identifying children at risk of VA.

Additionally, bioinformatics pathway analysis confirmed that the broader set of proteins is involved in the positive regulation of Janus kinase–signal transducer and activator of transcription signaling (involving IL-22 receptor subunit a1, IL-4, IL-20, IL10RA, LIF, and IL-2), inflammatory responses (IL-4, IL-20, LIF, and IL-2), and processes such as tyrosine phosphorylation, leukocyte differentiation, immunoglobulin G isotype switching, and protein phosphorylation regulation. These findings suggest that gluten-induced inflammation may already be active in early stages of the disease, including the initial phases of leukocyte differentiation, according to the investigators.

“Over a long follow-up on a gluten-containing diet, only 40% of these patients progressed to VA,” Auricchio and colleagues wrote. “Notably, 25%-30% of children with PCD even stop producing anti–tissue transglutaminase antibodies, and the others keep on producing autoantibodies but preserve a normal intestinal mucosa. Considering these data, the decision to address a patient with PCD on a gluten-free diet at time of diagnosis is quite critical.”

The researchers noted that this new model, with accuracy exceeding 95%, is well suited for routine use.

“Our previous model, based mainly on small intestinal mucosa features, moved a step toward the prediction of outcome but still required a mucosal biopsy, and the accuracy of prediction was not greater than 80%, which is somewhat uncertain for a lifelong clinical decision,” they wrote. In contrast, the present model “appears to be sufficient to immediately suggest a gluten-free diet in children with PCD, who are almost certainly committed to developing VA.”

The investigators called for long-term studies to validate their findings in other cohorts.

This study was supported by the TIMID project and Inflammation in Human Early Life: Targeting Impacts on Life Course Health (INITIALISE) by the Horizon Europe Program of the European Union. ■

Transitioning From Employment in Academia to Private Practice

A gastroenterologist's journey in starting from scratch

BY NEIL GUPTA, MD, MPH, FASGE

COURTESY DR. NEIL GUPTA

Dr. Neil Gupta, managing partner at Midwest Digestive Health & Nutrition, in Des Plaines, Illinois, explains his career choices.

After more than 10 years of serving in a large academic medical center in Chicago, Illinois, that was part of a national health care system, the decision to transition into private practice wasn't one I made lightly.

Having built a rewarding career and spent over a quarter of my life in an academic medical center and a national health system, the move to starting an independent practice from scratch was both exciting and daunting. The notion of leaving behind the structure, resources, and safety of the large health system was unsettling. However, as the landscape of health care continues to evolve, with worsening large structural problems within the US health care system, I realized that starting an independent gastroenterology practice — focused on trying to fix some of these large-scale problems from the start — would not only align with my professional goals but also provide the personal satisfaction I had failed to find.

As I reflect on my journey, there are a few key lessons I learned from making this leap — lessons that helped me transition from a highly structured employed physician environment to leading a thriving independent practice focused on redesigning gastroenterology care from scratch.

Lesson 1: Autonomy Opens the Door to Innovation

One of the primary reasons I left the employed physician setting was to gain greater control over my clinical practice and decision-making processes.

In a national health care system, the goal of standardization often dictates not only clinical care, but many "back end" aspects of the entire health care experience. We often see the things that are more visible, such as what supplies/equipment you use, how your patient appointments are scheduled, how many support staff members are assigned to help your practice, what electronic health record system you use, and how shared resources (like GI lab block time or anesthesia teams) are allocated.

However, this also impacts things we don't usually see, such as what fees are billed for care you are providing (like facility fees), communication systems that your patients need to navigate for help, human resource systems you use, and retirement/health benefits you and your other team members receive.

Standardization has two adverse consequences: 1) It does not allow for personalization, and as a result, 2) it suppresses innovation. Standard protocols can streamline processes, but they sometimes fail to account for the nuanced differences between patients, such as genetic factors, unique medical histories, or responses/failures to prior treatments. This rigidity can stifle innovation, as physicians are often bound by guidelines that may not reflect the latest advancements or allow for creative, individualized approaches to care. In the long term, an overemphasis on standardization risks turning health care into a one-size-fits-all model, undermining the potential for breakthroughs.

The transition was challenging at first, as we needed to engage our entire new practice with a different mindset now that many of us had autonomy for the first time. Instead of everyone just practicing health care the way they had done before, we took a page from Elon Musk and challenged every member of the team to ask three questions about everything they do on a daily basis:

- Is what I am doing helping a patient get healthy? (Question every requirement.)
- If not, do I still need to do this? (Delete any part of the process you can.)
- If so, how can I make this easier, faster, or automated? (Simplify and optimize, accelerate cycle time, and automate.)

The freedom to innovate is a hallmark of independent practice. Embracing innovation in every aspect of the practice has been the most critical lesson of this journey.

Lesson 2: Financial Stewardship Is Critical for Sustainability

Running an independent practice is not just about medicine — it's also about managing a business.

This was a stark shift from the large academic health systems, where financial decisions were handled by the "administration." In my new role as a business owner, understanding the financial aspects of health care was crucial for success. The cost of what patients pay for health care in the United States (either directly in deductibles and coinsurance or indirectly through insurance premiums) is unsustainably high. However, inflation continues to cause substantial increases in almost all the costs of delivering care: medical supplies, salaries, benefits, IT costs, etc. It was critical to develop a financial plan that accounted for these two macro-economic trends, and ideally helped solve for both. In our case, delivering high quality care with a lower cost to patients and payers.

We started by reevaluating our relationship with payers. Whereas being part of a large academic health system, we are often taught to look at payers as the adversary; as an independent practice looking to redesign the health care experience, it was critical for us to look to the payers as a partner in this journey. Understanding payer expectations and structuring contracts that aligned with shared goals of reducing total health care costs for patients was one of the foundations of our financial plan.

Offering office-based endoscopy was one innovation we implemented to significantly impact both patient affordability and practice revenue. By performing procedures like colonoscopies and upper endoscopies in an office setting rather than a hospital or ambulatory surgery center, we eliminated facility fees, which are often a significant part of the total cost of care. This directly lowers out-of-pocket expenses for patients and reduces the overall financial burden on insurance companies. At the same time, it allows the practice to capture more of the revenue from these procedures, without the overhead costs associated with larger facilities. This model creates a win-win situation: Patients save money while receiving the same quality of care, and the practice experiences an increase in profitability and autonomy in managing its services.

Lesson 3: Collaborative Care and Multidisciplinary Teams Can Exist Anywhere

One aspect I deeply valued in academia was the collaborative environment — having specialists across disciplines work together on challenging cases. In private practice, I was concerned that I would lose this collegial atmosphere. However, I quickly learned that building a robust network of multidisciplinary collaborators was achievable in independent practice, just like it was in a large health system.

In our practice, we established close relationships with primary care physicians, surgeons, advanced practice providers, dietitians,

behavioral health specialists, and others. These partnerships were not just referral networks but integrated care teams where communication and shared decision-making were prioritized. By fostering collaboration, we could offer patients comprehensive care that addressed their physical, psychological, and nutritional needs.

For example, managing patients with chronic conditions like inflammatory bowel disease, cirrhosis, or obesity requires more than just prescribing medications. It involves regular monitoring, dietary adjustments, psychological support, and in some cases, surgical intervention. In an academic setting, coordinating this level of care can be cumbersome due to institutional barriers and siloed departments. In our practice, some of these relationships are achieved through partnerships with other like-minded practices. In other situations, team members of other disciplines are employed directly by our practice. Being in an independent practice allowed us the flexibility to prioritize working with the right team members first, and then structuring the relationship model second.

Lesson 4: Technology Is a Vital Tool in Redesigning Health Care

When I worked in a large academic health system, technology was often seen as an administrative burden rather than a clinical asset. Electronic health records (EHR) and a lot of the other IT systems that health care workers and patients interacted with on a regular basis were viewed as a barrier to care or a cause of time burdens instead of as tools to make health care easier. As we built our new practice from scratch, it was critical that we had an IT infrastructure that aligned with our core goals: Simplify and automate the health care experience for everyone.

For our practice, we didn't try to re-invent the wheel. Instead we copied from other industries who had already figured out a great solution for a problem we had. We wanted our patients to have a great customer service experience when interacting with our practice for scheduling, questions, refills, etc. So we implemented a unified communication system that some Fortune 100 companies, with perennial high scores for customer service, used. We wanted a great human resource (HR) system that would streamline the administrative time it would take to handle all HR needs for our practice. So we implemented an HR information system that had the best ratings for automation and integration with other business systems. At every point in the process, we reminded ourselves to focus on simplification and automation for every user of the system.

Conclusion: A Rewarding Transition

The decision to leave academic medicine and start an independent gastroenterology practice wasn't easy, but it was one of the most rewarding choices I have made. The lessons I've learned along the way — embracing autonomy, understanding financial stewardship, fostering collaboration, and leveraging technology — have helped me work toward a better total health care experience for the community.

This journey has also been deeply fulfilling on a personal level. It has allowed me to build stronger relationships with my patients, focus on long-term health outcomes, and create a practice where innovation and quality truly matter. While the challenges of running a private practice are real, the rewards — both for me and my patients — are immeasurable. If I had to do it all over again, I wouldn't hesitate for a moment. If anything, I should have done it earlier. ▮

Dr. Gupta is managing partner at Midwest Digestive Health & Nutrition, in Des Plaines, Illinois. He has reported no conflicts of interest in relation to this article.

Treating GERD: Lifestyle Modifications vs Medication

Dear colleagues,
Gastroesophageal reflux disease (GERD) is a common reason for referral to gastroenterology. It affects a broad cross-section of our population and is often managed through a combination of lifestyle modifications and proton pump inhibitors (PPIs). However, in the era of PPIs, we must ask: Are lifestyle changes still necessary? And were they ever truly effective?

While PPIs are highly effective, concerns about their potential side effects frequently make headlines. Moreover, the financial burden of lifelong PPI use is a growing consideration. In this issue of Perspectives, Dr. Brijesh B. Patel and Dr. Juan D. Gomez Cifuentes explore these questions. Gomez Cifuentes highlights the benefits of lifestyle changes and identifies which strategies have proved most effective in his practice. Patel examines the ubiquitous use of PPIs and the challenges of sustaining adherence to lifestyle modifications. We hope these discussions will spark new ideas for managing GERD in your own practice.

We also welcome your thoughts on this topic — join the conversation on X at @AGA_GIHN.

Gyanprakash A. Ketwaroo, MD, MSc, is associate professor of medicine, Yale University, New Haven, and chief of endoscopy at West Haven VA Medical Center, both in Connecticut. He is an associate editor for GI & Hepatology News.


Dr. Ketwaroo

Do Lifestyle Changes Still Apply in the Treatment of GERD?

BY JUAN D. GOMEZ CIFUENTES, MD

Lifestyle changes are an essential part of managing gastroesophageal reflux disease (GERD). Increasingly, patients are asking about nonmedication approaches to control their symptoms. These lifestyle modifications can be categorized into four main areas: 1) weight loss, the cornerstone intervention, with significant symptom improvement observed after losing as little as 1.7 body mass index (BMI) points; 2) dietary modifications, which include both the traditional avoidance of trigger foods and the newer focus on a diet low in simple carbohydrates; 3) bedtime adjustments, strategies that include elevating the head of the bed, sleeping on the left side, using anti-reflux pillows, and avoiding late-night meals; 4) tobacco cessation, a key measure for reducing GERD symptoms and promoting overall health. I routinely discuss these changes with my patients, as they not only help manage GERD but also foster healthy habits and have a positive impact beyond the gastrointestinal tract.


Dr. Gomez Cifuentes

Weight loss is the most impactful lifestyle intervention for GERD. Research shows a clear linear improvement in symptoms with weight reduction. Traditionally, losing 10% of body weight is a widely accepted goal, extrapolated from other obesity-associated conditions. A reduction of 3.5 points of BMI led to significant symptom improvement in landmark studies, but also a modest reduction of 1.7 BMI points has been shown to provide symptom relief.[1] Abdominal circumference is another key metric used to track progress, as central obesity rather than BMI alone is strongly linked with GERD. Goals are typically set at less than 40 inches for men and 35 inches for women. Patients using glucagon-like peptide 1 (GLP-1) agonists should be informed that these medications may temporarily worsen GERD symptoms because of delayed gastric emptying; however in the long-term these symptoms are expected to improve once significant weight loss is achieved.

Food triggers vary among individuals, with common culprits including fatty meals, spicy foods, chocolate, tomato sauce, citrus fruits, and carbonated beverages. Patients tend to overemphasize diet elimination based on triggers and engage in strict diets. Patients are frequently afraid of these foods causing direct damage to the esophageal mucosa but

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Medical Therapy Is the Cornerstone of Effective GERD Treatment

BY BRIJESH B. PATEL, MD

Today, I saw Mr. S in the office for gastroesophageal reflux disease (GERD). He has been on a trial of proton pump inhibitors (PPIs) and has implemented several lifestyle modifications to manage his reflux. He shared his frustrations, saying, "Doctor, I've tried changing my diet, sleeping in a recliner, and adjusting the timing of my meals. I'm practically not enjoying food anymore, and these lifestyle changes have affected my quality of life. Despite all this, I still wake up in the middle of the night with a 'horrible taste' in my mouth, and it's ruining my sleep."


Dr. Patel

Later that day, during a discussion with my trainees, one posed an important question: "What about lifestyle measures in the treatment of GERD?" This is a common query in both clinical and academic settings. GERD, with a prevalence estimated at ~20%, is often underreported as many patients begin self-medicating with over-the-counter acid suppressive therapies before seeking medical care. For gastroenterologists, PPIs, histamine-2 receptor antagonists (H2RAs), and now potassium-competitive acid blockers (PCABs) form the cornerstone of GERD management.

When I lecture medical students, residents, and fellows about GERD, I emphasize a standard approach: initiating an 8- to 12-week trial of PPIs followed by reassessment. I also stress the importance of combining medical therapy with lifestyle measures. However, the question remains: How adherent are our patients to these lifestyle changes? Similarly, how effectively are trainees integrating the value of lifestyle modifications into their practice? As an academic gastroenterologist, I can teach the theory, but is it being translated into real-world patient care?

The advent of PPIs has been a game changer for managing GERD symptoms and preventing disease progression. PPIs are the backbone of treatment in both gastroenterology and primary care, and they have profoundly improved patients' quality of life. Most of my patients who present with GERD — whether due to uncontrolled reflux or acid exposure — have already been on a trial of PPIs before seeing me. My role often involves optimizing their

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the hypothesis is that these triggers worsen GERD by increasing transient relaxations of the lower esophageal sphincter. The evidence behind this and diet elimination based on triggers has always been weak. In my practice, I encourage patients to follow a diet low in simple carbohydrates. Simple carbohydrates are present in highly processed food; the average Western diet contains ~140 g/day. In a trial, a diet low in simple sugars (monosaccharides and disaccharides < 62 g/day) without reducing total daily calories, objectively improved total acid exposure time in a pH study.[2]

Thanks to gravity, nocturnal GERD symptoms are the culprit of many restless nights in these patients. I recommend avoiding food 3 hours before lying down. Since the stomach empties approximately 90% of its contents after 4 hours, waiting longer is not recommended and may result in hunger, making it harder to fall asleep. Sleeping on the left side, which takes advantage of the gastric anatomy, has proved to objectively decrease nocturnal acid exposure time, though some patients may find it challenging to maintain this position all night.[3]

Elevating the head of the bed is another effective intervention, but it must involve raising the upper body from the waist. Patients should avoid stacking ordinary pillows as this will elevate only the neck and place the body in an unnatural position for sleeping. The most effective strategies are putting blocks/bricks under the feet of the bed, using a bed wedge between the mattress and the box spring, or using an adjustable bed frame. There are two types of pillows that have been shown to improve nocturnal GERD symptoms: the classic wedge pillows and the more expensive Medcline reflux relief system®. The Medcline pillow has a dual mechanism that elevates the upper body but also keeps the body on the left side position.[4]

Tobacco cessation is strongly recommended. Tobacco worsens GERD symptoms by reducing the lower esophageal sphincter pressure and decreasing saliva production which is one of the key components of the normal esophageal acid barrier. Moreover, it is a known risk factor for esophageal cancer. Alcohol has a variety of negative health impacts and decreasing alcohol intake is advised; however, the link between alcohol and GERD symptoms is less robust, especially in patients with low occasional consumption.

In summary, lifestyle modifications play a pivotal role in managing GERD symptoms, offering patients effective, nonpharmacologic strategies to complement medical treatments. Weight loss remains the cornerstone, with even modest reductions in BMI showing significant symptom relief. Dietary adjustments, particularly adopting a low–simple carbohydrate diet, provide an evidence-based approach. Various bedtime interventions are available to improve nocturnal GERD symptoms. Finally, tobacco cessation is essential, not only for GERD symptom relief but also for overall health. By integrating these lifestyle changes into their routine, patients can improve GERD symptoms while building healthy habits. ■

Dr. Gomez Cifuentes is vice-chair in the section of gastroenterology at Presbyterian Healthcare Services, Albuquerque, New Mexico. He declares no conflicts of interest.

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timing of PPI administration, addressing incorrect usage, and reinforcing the importance of adherence. In some cases, I incorporate H2RAs as adjunctive therapy for patients who fail to respond adequately to PPIs, particularly when objective disease activity is confirmed through pH studies. These studies also highlight how challenging it is for many patients to maintain a refluxogenic-free lifestyle.

Lifestyle modifications should supplement and support GERD management. Regardless of medical specialty, lifestyle measures should be the first line of treatment. However, adherence and effectiveness vary widely. In reality, achieving sustained weight loss, meal timing adjustments, and dietary modifications (eg, eliminating trigger foods like red wine, chocolate, coffee, and tomato-based sauces) is a significant challenge for patients. While these measures can reduce the need for PPIs in some cases, they are rarely sufficient as standalone treatments. Until lifestyle modifications are consistently and sustainably incorporated into daily routines, acid-suppressive therapy will remain the mainstay of GERD management.

As for newer therapies, PCABs are now Food and Drug Administration approved for treating GERD. Early efficacy data suggest that PCABs are noninferior to PPIs, with promising results in managing Los Angeles Class C and D esophagitis and maintaining symptom-free days. However, like PPIs, PCABs are associated with potential adverse effects, including *Clostridioides difficile* colitis, impacts on bone health, renal impairment, and mineral deficiencies. While these risks must be carefully discussed with patients, the benefits of medical therapy far outweigh the risks, especially for those with erosive esophagitis, Barrett's esophagus, or a high-risk profile for esophageal cancer. In such cases, medical therapies provide superior disease control compared to lifestyle measures, supported by both subjective and objective data.

Managing GERD requires a multipronged approach. Relying solely on lifestyle measures rarely provides complete benefit, as restrictive dietary regimens are difficult to sustain long term. Like many, I can maintain a restrictive diet temporarily but find it unsustainable over time. Conversely, adherence to daily or twice-daily medications tends to be much higher than compliance with multi-level lifestyle changes (eg, restrictive diets, weight loss, and trigger-food avoidance).

Our therapeutic arsenal for GERD continues to expand, enabling more effective management of patients with uncontrolled acid reflux. While I will continue to counsel patients and educate trainees on the value of lifestyle modifications, I emphasize the importance of adherence to timely medical therapy — whether with PPIs, H2RAs, or PCABs — as the cornerstone of effective GERD treatment. ■

Dr. Patel is associate program director in the division of digestive diseases & nutrition, at USF Health, Tampa, Florida. He declares no conflicts.

Score Effectively Predicts GI Bleeding Risk Post PCI

BY CAROLYN CRIST

FROM ACG 2024

PHILADELPHIA — Gastrointestinal (GI) bleeding after percutaneous coronary intervention (PCI) among patients on dual-antiplatelet therapy (DAPT) remains risky in terms of morbidity and mortality, but the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score could help predict that risk, according to a study presented at the American College of Gastroenterology (ACG) 2024 Annual Scientific Meeting.

In a predominantly Hispanic population in Texas, 2.5% of post-PCI patients on DAPT had GI bleeding in the first year. The PRECISE-DAPT score helped to predict GI bleeding among high-risk and moderate-risk patients.

"Our study established that the PRECISE-DAPT score possesses a moderate predictive accuracy not only for overall bleeding risk but also specifically for gastrointestinal bleeding," said lead author Jesus Guzman, MD, a gastroenterology fellow at the Texas Tech University Health Sciences Center El Paso.

Current guidelines from the American College of Cardiology and American Heart Association recommend DAPT for 6-12 months post PCI, with consideration for shorter durations in patients with lower ischemic risks but higher bleeding risks.

"Interestingly, some of these patients were on DAPT for more than 2 years, which goes beyond the guidelines," he said. "In this patient population, this has to do with them being lost to follow-up and getting reestablished, and they kept refilling their prescriptions."

Dr. Guzman

Among the 39 GI bleeds, 41% were lower GI bleeds, 28% were upper GI bleeds, 15% were small bowel bleeds, and 15% were undetermined. The most frequent etiology was colon cancer, accounting for 18% of bleeds, followed by 15% for gastric ulcers, 10% for diverticular bleeds, and 10% for hemorrhoidal bleeds.

Guzman and colleagues conducted a retrospective cohort study of patients receiving DAPT after PCI from 2014 to 2021. They looked for GI bleeding rates at 1 year and across the duration of the study period, as well as endoscopic indications, findings, concurrent antiplatelet therapy, and the primary cause of bleeding.

In addition, the research team evaluated the predictive value of the PRECISE-DAPT score, which categorizes patients based on low risk (≤ 17), moderate risk (18-24), and high risk (≥ 25) for bleeding. The score aims to optimize the balance between bleeding and ischemic risks, Guzman said, by incorporating five factors: age, creatinine clearance, hemoglobin, white blood cell count, and history of spontaneous bleeding.

Among 1067 patients, 563 (57.9%) received clopidogrel and 409 (42%) received ticagrelor. The overall cohort was 66.6% men and 77.1% Hispanic, and had a mean age of 62 years.

The GI bleeding rate was 2.5% at 1-year post PCI among 27 patients and 3.7% for the study duration among 39 patients, with a median follow-up of 2.2 years.

Among the 39 GI bleeds, 41% were lower GI bleeds, 28% were upper GI bleeds, 15% were small bowel bleeds, and 15% were undetermined. The most frequent etiology was colon cancer, accounting for 18% of bleeds, followed by 15% for gastric ulcers, 10% for diverticular bleeds, and 10% for hemorrhoidal bleeds.

In general, analyses indicated no significant differences in GI bleeding between patients on clopidogrel (21.2%) and those on ticagrelor (19.2%).

However, the odds of GI bleeding were significantly higher in patients with high-risk PRECISE-DAPT scores (odds ratio [OR], 2.5) and moderate-risk scores (OR, 2.8) than in those with low-risk scores. The majority of patients without GI bleeding had scores < 17, whereas the majority of patients with GI bleeding had scores > 24. An optimal threshold for the PRECISE-DAPT score was identified as ≥ 19.

"When patients on DAPT present with GI bleeding, it can be a clinical conundrum for gastroenterologists and cardiologists, especially when it can be a life-or-death event, and stopping DAPT can increase risk of thrombosis," said Jeff Taclob, MD, a hepatology fellow at the University of Tennessee Health Science Center in Memphis. Taclob, who wasn't involved with the study, attended the conference session.

"In this population in El Paso, in particular, many patients don't have adequate health care, may be lost to follow-up, and get their prescriptions filled elsewhere, such as Juárez, Mexico," he said. "Then they come in with this life-threatening bleed, so we need to focus more on their risks."

'Interestingly, some of these patients were on DAPT for more than 2 years, which goes beyond the guidelines. In this patient population, this has to do with them being lost to follow-up and getting reestablished, and they kept refilling their prescriptions.'

Paying attention to specific patient populations, cultures, and values remains important for patient communication and clinical decision-making, Taclob noted.

"In this population of older men, there's often a persona where they don't want to seek help," he said. "DAPT criteria could differ in other populations, but here, the PRECISE-DAPT score appeared to help."

The study was awarded the ACG Outstanding Research Award in the GI Bleeding Category (Trainee). Guzman and Taclob reported no relevant disclosures. ■

A Patient-Centered Document

Guidelines *from page 1*

coauthor and gastroenterologist Manasi Agrawal, MD, MS, an assistant professor of medicine at Icahn School of Medicine at Mount Sinai in New York City, said in an interview.

"We provide a practical guidance based on best-available evidence to make it easy for the treating clinician to make informed choices from the multiplicity of available treatments for UC," added guidelines coauthor Ashwin Ananthakrishnan, MBBS, MPH, AGAF, a gastroenterologist at Massachusetts General Hospital in Boston.

Dr. Agrawal

Dr. Ananthakrishnan

The comprehensive, patient-centered document comes with this caveat from the AGA panel: "These guidelines are meant to be broad recommendations for management of patients with moderate to severe UC and are not intended to address the intricacies of individual patients," they wrote. "Provider experience and patient values and preferences can inform treating providers and patients to reasonably choose alternative treatment options."

One gastroenterologist who has been eagerly awaiting these guidelines but not involved in the panel is James D. Lewis, MD, MSCE, AGAF, a professor of medicine and epidemiology at Perelman School of Medicine at the University of Pennsylvania, Philadelphia. "The choice of medications for moderately to severely active UC has expanded tremendously in the past few years," he said in an interview. "This resulted in the dismantling of the historical therapeutic pyramid." And while there are many more treatment options, knowing which medication to use for which patient and in which sequence has become much more complicated.

"These guidelines will be extremely helpful for clinicians trying to navigate this new era of UC care," he said.

The guidelines also outline implementation considerations for optimal use in different scenarios. "Key considerations include patient-related factors such as age, frailty, other health conditions, consideration for pregnancy, patient preferences, and access to healthcare," Agrawal said.

Specifics

Overall, the guidance recommends advanced or immunomodulatory therapy after failure of 5-ASAs rather than a step-up approach. Moderate to severe disease is defined as a Mayo endoscopic severity subscore of 2 or 3 (J Crohns Colitis. 2015 Oct;9[10]:846-852).

The recommendation may also apply to mild disease in the presence of a high burden of inflammation and a poor prognosis or steroid dependence or resistance.

The AGA guideline panelists took account of differences in treatment efficacy between drugs within the same therapeutic class and made their recommendations by specific drugs rather than therapy class.

Based on varying degrees of evidence certainty, the AGA recommends or suggests the following management specifics in adult outpatients with moderate to severe disease:

- Any of the following is recommended over no treatment: infliximab (Remicade), golimumab (Simponi), vedolizumab (Entyvio), tofacitinib (Xeljanz), upadacitinib (Rinvoq), ustekinumab (Stelara), ozanimod (Zeposia), etrasimod (Velsipity), risankizumab (Skyrizi), and guselkumab (Tremfya).
- Adalimumab (Humira), filgotinib (Jyseleca), and mirikizumab (Omvoh) are suggested over no treatment.
- Biosimilars to infliximab, adalimumab, and ustekinumab can be considered of equivalent efficacy to their originator drugs.
- For patients naive to advanced therapies, the AGA panel proposes using a higher-efficacy medication (eg, infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, and guselkumab) or an intermediate-efficacy medication (golimumab, ustekinumab, tofacitinib, filgotinib, and mirikizumab) rather than a lower-efficacy medication such as adalimumab.
- In patients previously exposed to advanced therapy, particularly tumor necrosis factor (TNF)–alpha antagonists, the panel suggests using a higher-efficacy medication (tofacitinib, upadacitinib, and ustekinumab) or an intermediate-efficacy agent (filgotinib, mirikizumab, risankizumab, and guselkumab) over a lower-efficacy medication (adalimumab, vedolizumab, ozanimod, and etrasimod).
- The panel suggests against the use of thiopurine monotherapy for inducing remission but suggests thiopurine monotherapy over no treatment for maintenance of (typically corticosteroid-induced) remission.
- The panel suggests against the use of methotrexate monotherapy for induction or maintenance of remission.
- Infliximab, adalimumab, and golimumab in combination with an immunomodulator are suggested over monotherapy.
- The panel makes no recommendation for or against non-TNF antagonist biologics in combination with an immunomodulator over non-TNF biologics alone.
- For patients in corticosteroid-free clinical remission for at least 6 months on combination therapy with TNF antagonists and immunomodulators, the panel suggests against withdrawing TNF antagonists but makes no recommendation for or against withdrawing immunomodulators.
- For those who have failed 5-ASAs and have escalated to immunomodulators or advanced therapies, the panel suggests stopping these agents. It suggests the early use of advanced therapies and/or immunomodulator therapy rather than gradual step-up after failure of 5-ASAs.

Dr. Lewis

According to Lewis, the guidance will be useful to both community physicians and highly specialized gastroenterologists. "While few practicing physicians will be able to commit the entirety of the classifications in this guideline to memory, the tool is a quick reference resource to help providers and patients to choose between the many options," he said.

However, he noted that not all patients and providers may have the same priorities as the guidelines. "There are a few nuances to the methods of the AGA guidelines. For example, the panel prioritized efficacy over safety because the incidence of serious adverse events secondary to medications is relatively rare."

Lewis also noted that the way the panel classified higher-, intermediate-, and lower-efficacy medications sometimes produced surprising results. "For example, among patients naive to advanced therapies, the IL [interleukin]–23 inhibitors risankizumab and guselkumab were classified as higher efficacy, while the IL-12/23 inhibitor ustekinumab was considered intermediate efficacy," he said. "These were reversed for patients with prior exposure to advanced therapies, where ustekinumab was considered higher efficacy and all three IL-23 inhibitors were considered intermediate efficacy."

The Future

The panel identified several knowledge gaps that future studies should address. These include a paucity of head-to-head comparison trials, including active comparators to accurately inform positioning of different treatments and therapeutic mechanisms.

The panelists also noted a literature gap on the efficacy of different therapies in the setting of failure or intolerance to non-TNF antagonist advanced therapy, which could be relevant to drugs that may have a greater overlap in their therapeutic mechanisms — for instance, anti-trafficking agents.

They pointed to a paucity of data on how predictive models can inform future treatment selection in the real-world setting. "There is clearly a need for identifying biomarkers predictive of response to individual therapies, to facilitate optimal choice of therapies," they wrote.

The panel also recognized that novel therapeutic strategies may soon be in use, including combination advanced therapy or episodic use of nonimmunogenic advanced therapies such as small molecules. "Further primary data are required to accurately inform the positioning of such strategies," they wrote.

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