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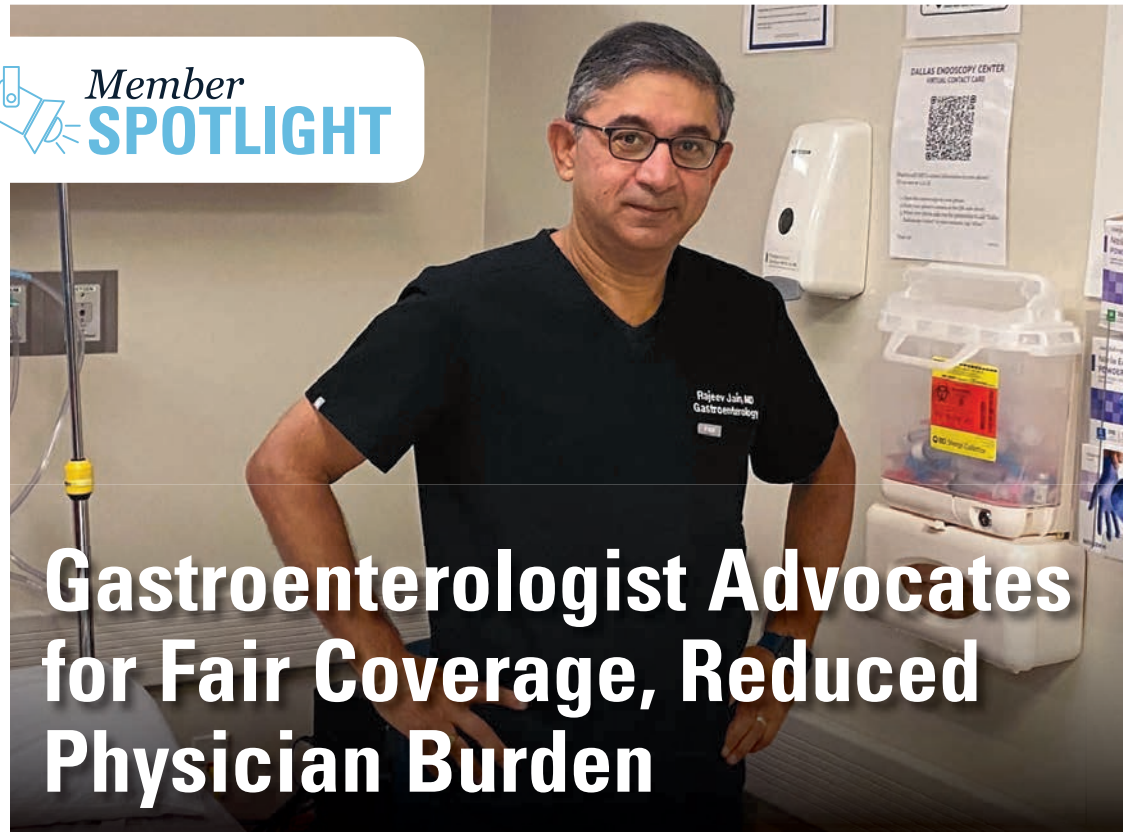
Techniques for endoscopic management of benign gallbladder disease outlined.

GI & Hepatology News

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Member SPOTLIGHT



Gastroenterologist Advocates for Fair Coverage, Reduced Physician Burden

Dr. Rajeev Jain of Texas Digestive Disease Consultants has spoken out to support patients' access to care.

BY JENNIFER LUBELL

MDedge News

Faced with an opportunity to advocate for patients, Rajeev Jain, MD, AGAF, is never afraid to speak up. He recently spoke out publicly against a major payer's new advance notification process for colonoscopy and endoscopy procedures, cautioning it was a glidepath toward far-reaching prior authorization requirements.

UnitedHealthcare (UHC) plans to collect a larger scope of data for this new policy, "which I fear will disrupt and deny patients' access to lifesaving care," Dr. Jain, a gastroenterologist with Texas Digestive Disease Consultants and a member of the American

Gastroenterological Association's (AGA) Prior Authorization Reform Task Force, wrote in an opinion piece in the *Dallas Morning News*.

Insurance coverage should be fair to the end goal of taking good care of patients, said Dr. Jain. "And if they're putting processes in place, which are solely to be an impediment to excellent care, then that's not right."

Through his extensive participation in AGA panels and other influential groups, Dr. Jain has sought to improve clinical practice and reduce physician burnout. As Director and now Chair of the Board of Directors of the American Board of Internal Medicine (IBIM), Dr. Jain has played an influential role in

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Who Is Helped by AI Use During Colonoscopy?

BY MARILYNN LARKIN

Artificial intelligence (AI) holds the promise of identifying premalignant and advanced malignant lesions during colonoscopy that might otherwise be missed.

Is it living up to that promise?

It seems that depends on where, how, and by whom it's being implemented.

Clinical Trials vs the Real World

The majority of randomized clinical trials of AI use conducted worldwide "clearly show an increase in the adenoma detection rate (ADR) during colonoscopy," Prateek Sharma, MD, a gastroenterologist at the University of Kansas Cancer Center, Kansas City, told this news organization. "But the real-world results have been quite varied; some show improvement, and others don't."

Dr. Sharma is coauthor of a recent pooled analysis of nine randomized controlled trials on the impact of AI on colonoscopy surveillance after polyp removal (*Clin Gastroenterol Hepatol*. 2023 Apr. doi: 10.1016/j.cgh.2022.08.022). It found that AI use increased the proportion of patients requiring intensive surveillance by approximately 35% in the United States and 20% in Europe (absolute increases of 2.9% and 1.3%, respectively).

"While this may contribute to improved cancer prevention, it significantly adds patient burden and healthcare costs," the authors concluded.

A recent retrospective analysis (*Clin Gastroenterol Hepatol*. 2023 Sep. doi: 10.1016/j.cgh.2023.09.008) of staggered implementation of a computer-aided

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE



LETTER FROM THE EDITOR

Moving the Field FORWARD

As an organization, AGA has invested heavily in programs and initiatives to support the professional development of its members across career stages. This includes programs such as the AGA-AASLD Academic Skills Workshop (in which I was fortunate to participate in 2016), Women's Leadership and Executive Leadership Conferences (with the Midwest Women in GI Regional Workshop taking place later this month), and the AGA Research Foundation Awards Program, which distributes over \$2 million in funding annually to support promising early career and senior investigators.



Dr. Adams

AGA's Fostering Opportunities Resulting in Workforce and Research Diversity (FORWARD) Program, which was first funded by the National Institutes of Health in 2018 and is focused on improving the diversity of the GI research workforce, is another shining example. Led by Dr. Byron Cryer and Dr. Sandra Quezada, the program recently welcomed its 3rd cohort of participants, including 14 mentees and 28 senior and near-peer mentors.

As a longstanding AGA member, I am proud to be a part of an organization that values diversity and invests in cutting-edge programs to support development of future leaders in our field across multiple domains. We are pleased to frequently highlight these programs in the pages of *GI &*

Hepatology News, and hope you enjoy learning more about each of these initiatives in future issues.

In this month's issue of *GIHN*, we highlight AGA's newest Clinical Practice Guideline focused on management of pouchitis. We also report on the results

AGA's Fostering Opportunities Resulting in Workforce and Research Diversity (FORWARD) Program was first funded by the National Institutes of Health in 2018 and is focused on improving the diversity of the GI research workforce.

of a recent RCT published in the *New England Journal of Medicine* demonstrating the efficacy of thalidomide as a treatment for recurrent bleeding due to small-intestinal angiodysplasia and summarize other key journal content impacting your clinical practice. In our February Member Spotlight, we feature Dr. Rajeev Jain of Texas Digestive Disease Consultants, a former AGA Governing Board member, and learn about his advocacy work to improve patient care and reduce physician burnout through insurance coverage and MOC reform. We hope you enjoy this, and all the exciting content included in our February issue! ■

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

AGA Members Save on Registration for DDW® 2024

Follow your own path to better outcomes for patients with GI diseases at Digestive Disease Week® (DDW) 2024, the world's largest and most comprehensive gathering of gastroenterology clinicians, researchers, and industry. Registration and housing are now open, and AGA members can save up to \$380 on registration fees. Discounted registration rates are also available through the March 13 early bird deadline. AGA member trainees, students, residents and postdoctoral fellows can register for free through this date. Visit ddw.org/register to join us.

This year, DDW takes place May 18-21, in Washington, D.C., and online. Whether you work in patient care, research, training, or academia, you'll find content tailored to your essential role at every step.

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IBS Meta-Analysis: Some Support for Mesalamine

BY WILL PASS

MDedge News

FROM CLINICAL GASTROENTEROLOGY
AND HEPATOLOGY

Certain patients with irritable bowel syndrome (IBS) may benefit from treatment with mesalamine, although the quality of evidence supporting this strategy remains low, according to a recent systematic literature review and meta-analysis.

Global IBS symptoms improved significantly across the entire population; however, a subgroup analysis suggested that mesalamine may be most beneficial for patients who present with diarrhea, providing support for a large clinical trial

in this patient population, reported lead author Vivek C. Goodoory, MBChB, of St. James's University Hospital, Leeds, England, and colleagues.



Dr. Goodoory

Some patients with IBS may

present with low-grade inflammation in the intestine, offering theoretical grounds for prescribing mesalamine, which is typically used for treating ulcerative colitis, the investigators wrote in *Clinical Gastroenterology and Hepatology* (2023 Feb 27. doi: 10.1016/j.cgh.2023.02.014). Yet previous randomized controlled trials (RCTs)

Advancements in the understanding of irritable bowel syndrome (IBS) pathophysiology have led to new pharmacological agents and guidelines on the delivery of patient-specific IBS care. However, treatments targeting specific IBS mechanisms including altered immune responses, barrier dysfunction, and low-grade inflammation are lacking.

In a systematic review and meta-analysis, Goodoory et al. find that pooled results from six randomized controlled trials suggest efficacy with mesalamine, an anti-inflammatory agent, for global IBS symptoms with subgroup analyses further suggesting efficacy in IBS with diarrhea. However, results are tempered by the overall low quality of evidence and lack of benefit for abdominal pain or bowel habits. Notably, the only study rated as low risk of bias did not find mesalamine to be effective. Thus, these findings cannot yet be used to inform clinical decision-makers.

Mesalamine's practical advantage lies in its availability as an effective treatment for inflammatory bowel disease (IBD). Based on indirect evidence,

evaluating mesalamine for IBS have yielded mixed results, and a meta-analysis (*Aliment Pharmacol Ther*. 2022 Sep;56[6]:968-79) showed that mesalamine offered no benefit.

According to Dr. Goodoory and colleagues, however, that meta-analysis fell short since it "only pooled mean symptom scores, rather than the proportion of patients in each trial experiencing an improvement in symptoms, and did not appear to include data from all available RCTs." Furthermore, they

noted that this prior study lacked subgroup analyses conducted based on IBS subtype or postinfection status.

"We, therefore, conducted a contemporaneous meta-analysis to examine the efficacy and safety of mesalamine in IBS addressing these deficits in knowledge," the investigators wrote.

Their meta-analysis included 820 patients from eight RCTs published between 2009 and 2022. Efficacy and safety were evaluated via dichotomous assessments of

mesalamine may also be used to treat a spectrum of diverticular diseases (e.g., segmental colitis associated with diverticulitis [SCAD], symptomatic uncomplicated diverticulosis [SUDD]). In some clinical scenarios, the distinctions between IBS and SCAD, SUDD, or quiescent IBD may be challenging to make. These observations raise the question of whether mesalamine could be considered for IBS-type symptoms in patients with overlapping IBD or diverticular disease.

Still, further study is warranted. Such future work will benefit from including well-phenotyped patients and novel biomarkers with the ability to identify individuals in whom inflammatory mechanisms contribute to IBS symptoms.

Andrea Shin, MD, is based in the Division of Digestive Diseases at the University of California Los Angeles. She is a member of the editorial board for *Clinical Gastroenterology and Hepatology*, and the Scientific Communications Advisory Board for IBS-C. For a complete list of disclosures, see the online version of this article.



Dr. Shin

global IBS symptoms, bowel habit or stool frequency, abdominal pain, and adverse events. Two subgroup analyses were planned to evaluate responses based on postinfection status and predominant stool pattern.

Unlike the previous meta-analysis, Dr. Goodoory and colleagues detected a potential signal for efficacy.

Across all patients, mesalamine was associated with significant improvement in global IBS symptoms, compared with placebo (relative

See **IBS** • Continued on following page

Rebranding NAFLD: Correcting Flawed Conventions

BY WILL PASS

MDedge News

FROM GASTROENTEROLOGY

Nonalcoholic fatty liver disease (NAFLD) should now be referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), according to a recent commentary by leading hepatologists.

This update, which was determined by a group of 236 panelists from 56 countries, is part of a broader effort to rebrand "fatty liver disease" as "steatotic liver disease" (SLD), reported lead author Alina M. Allen, MD, of Mayo Clinic, Rochester, Minnesota, and colleagues.

Writing in *Gastroenterology* (2023 Nov 8. doi: 10.1053/j.gastro.2023.11.007), they described a range of reasons for the nomenclature changes, from the need for better characterization of disease subtypes, to the concern that the term

"fatty" may be perceived as stigmatizing by some patients.

"The scientific community and stakeholder organizations associated with liver diseases determined there was a need for new terminology to cover liver disease related to alcohol alone, metabolic risk factors (until recently termed NAFLD/nonalcoholic steatohepatitis [NASH]) alone, the combination of alcohol and metabolic risk factors, and hepatic steatosis due to other specific etiologies," the authors wrote.

Naming conventions in this area have been flawed since inception, Dr. Allen and colleagues wrote, noting that "nonalcoholic" is exclusionary rather than descriptive, and is particularly misplaced in the pediatric setting. These shortcomings could explain why the term "NASH" took more than a decade to enter common usage, they suggested, and why the present effort is not the first of its kind.

"There have been several movements to change the nomenclature [of NAFLD], including most recently to 'metabolic dysfunction-associated fatty liver disease' (MAFLD), a term that received limited traction," the authors wrote.

Still, a change is needed, they added, as metabolic dysfunction is becoming increasingly common on a global scale, driving up rates of liver disease. Furthermore, in some patients, alcohol consumption and metabolic factors concurrently drive steatosis, suggesting an intermediate condition between alcohol-related liver disease (ALD) and NAFLD that is indescribable via current naming conventions.

SLD (determined by imaging or biopsy) now comprises five disease subtypes that can be determined via an algorithm provided in the present publication.

If at least one metabolic criterion is present,

See **NAFLD** • Continued on following page

Inflammatory Responses to a Common Food Additive May Depend On the Microbiome

BY WILL PASS

MDedge News

FROM CELLULAR AND MOLECULAR
GASTROENTEROLOGY AND HEPATOLOGY

Inflammatory responses to the food additive carboxymethylcellulose (CMC) may depend on the unique characteristics of an individual's microbiome, according to recent research.

These findings suggest that CMC, which is commonly used as a thickener and emulsifier to improve texture and shelf life of food, could potentially trigger chronic inflammation in genetically prone individuals, although more work is needed to pinpoint the exact microbiota involved, reported lead author Noémie Daniel, PhD, of the French National Institute of Health and Medical Research (INSERM), Paris, and colleagues.

"Preclinical work has shown that [CMC] consumption detrimentally impacts the intestinal microbiota in a way that promotes chronic inflammation," the investigators wrote in a research letter in *Cellular and Molecular Gastroenterology and Hepatology* (2023 Nov 4. doi: 10.1016/j.jcmgh.2023.11.001).

They published the results of a randomized, double-blind controlled trial (*Gastroenterology*. 2022 Mar;162[3]:743-56) that showed that the seven individuals exposed to a CMC-supplemented diet had "significant alterations in microbiota composition and metabolome" compared with the nine control subjects.

Yet responses to CMC varied widely. In the

The consumption of highly processed foods, enriched with food additives, is associated with an increased risk of developing inflammatory bowel disease (IBD). Alteration of the intestinal barrier and microbiota encroachment on epithelial cells is thought to be one of the mechanisms leading to inappropriate mucosal immune activation in response to food additive intake. However, we still do not know why some exposed individuals develop IBD while others do not. The findings of Daniel and colleagues suggest that proinflammatory sensitivity to the food additive carboxymethylcellulose (CMC) is primarily dependent on the composition of the gut microbiota, and that this sensitivity can be, at least partially, transferable, using fecal microbiota transfers in a mouse model of IBD. In particular, they identified 11 taxa of the host basal microbiota associated with the development of intestinal inflammation in response to CMC.

From the clinician's point of view, this work, which needs to be confirmed by larger interventional studies, opens the way to practical, personalized nutritional advice based on the

patient's fecal microbiota signature, identifying patients at higher risk of developing deleterious inflammatory responses after exposure to CMC-containing foods. Moreover, as microbiota encroachment is also observed in other chronic diseases associated with the Western lifestyle, such as metabolic diseases and diabetes, these findings may also be of great interest in other pathological contexts.

Finally, this study also illustrates the relevance of systematically assessing the impact of food additives and emulsifiers on the gut

microbiota and intestinal physiology in order to evaluate their safety using translational approaches similar to those applied by Daniel and colleagues.

Nicolas Benech, MD, PhD, is an assistant professor at the Lyon 1 University and Gastroenterology department, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France, the director of the Lyon Fecal Microbiota transplantation Center, and cofounder of the Lyon GEM Microbiota Study Group. He has no conflicts.



Dr. Benech

treatment group, some participants were relatively insensitive to CMC, while two participants had "stark alterations" in their microbiome.

"Such CMC sensitivity was not associated with

overt signs of intestinal inflammation but nonetheless might mark proneness to chronic inflammation, compelling us to better understand

Continued on following page

IBS • Continued from previous page
risk [RR], 0.86; 95% CI, 0.79-0.95). However, no significant improvements were detected for abdominal pain or bowel habit/stool frequency.

A subgroup analysis of patients exhibiting IBS with diarrhea showed significantly greater improvements in global IBS symptoms for mesalamine versus placebo (RR, 0.88; 95% CI, 0.79-0.99). This subgroup showed no improvements in abdominal pain or bowel habit/stool frequency.

Subgroup analyses for patients with constipation or mixed bowel habits, or based on postinfection status, revealed no significant differences, although the investigators noted that relevant data were limited.

Mesalamine appeared to be well tolerated. Across five studies reporting adverse events, 43.5% of patients receiving mesalamine reported any adverse event, compared with 41.4% of patients on

placebo. The RR of experiencing an adverse event in those taking mesalamine was 1.20 (95% CI, 0.89-1.63), which was not statistically significant.

"There was no evidence of heterogeneity between studies in most of our analyses, but only one trial was at low risk of bias across all domains, and there were insufficient studies to assess for funnel plot asymmetry," Dr. Goodyoy and colleagues wrote. "Based on these limitations of the evidence," they continued, "our confidence in the results of the meta-analysis would be low, and further large trials at low risk of bias would be informative."

Specifically, the investigators suggested an RCT recruiting only patients with IBS with diarrhea, and reporting efficacy according to postinfection status.

One coauthor reported research funding from Tillotts Pharma and Dr Falk Pharma UK. The remaining authors reported no conflicts. ■

NAFLD • Continued from previous page
but no other causes of steatosis, then that patient has MASLD. The three other metabolic subtypes include MetALD (2-3 drinks per day for women and 3-4 drinks per day for men), ALD (more than 3 drinks per day for women and more than 4 drinks per day for men), and monogenic miscellaneous drug-induced liver injury (DILI).

Patients without metabolic criteria can also be classified with monogenic miscellaneous DILI with no caveat, whereas patients with metabolic criteria need only consume 2 or 3 drinks per day for women or 3-4 drinks per day for men, respectively, to be diagnosed with ALD.

Finally, patients with no metabolic criteria or other cause of steatosis should be characterized by cryptogenic SLD.

"While renaming and redefining the disease was needed, the implementation is not without challenges," Dr. Allen and colleagues wrote. "A more complex classification may add

confusion in the mind of nonhepatology providers when awareness and understanding of the implications of SLD are already suboptimal."

Still, they predicted that the new naming system could lead to several positive outcomes, including improved SLD screening among individuals with metabolic risk factors, more accurate phenotyping of patients with moderate alcohol consumption, increased disease awareness in nonhepatology practices, and improved multidisciplinary collaboration.

Only time will tell whether these benefits come to fruition, Dr. Allen and colleagues noted, before closing with a quote: "In the words of Jean Piaget, the developmental psychologist of the 20th century, who coincidentally died the year the term NASH was coined, 'Scientific knowledge is in perpetual evolution; it finds itself changed from one day to the next.'"

The authors disclosed no conflicts of interest. ■

AGA Publishes New Pouchitis Management Guideline

BY WILL PASS

MDedge News

FROM THE AMERICAN
GASTROENTEROLOGICAL ASSOCIATION

The American Gastroenterological Association (AGA) has published a new clinical practice guideline on the management of pouchitis and inflammatory pouch disorders.

The guidance document, authored by Edward L. Barnes, MD, of the University of North Carolina at Chapel Hill and colleagues, includes 11 conditional recommendations that steer usage of probiotics, antibiotics, and immunosuppressive therapies in patients with these conditions, which occur most often after restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) for ulcerative colitis (UC).

“Multiple strategies have been utilized in the treatment and prevention of pouchitis and inflammatory pouch conditions, including antibiotics, probiotics, corticosteroids, and advanced immunosuppressive therapies including biologics and oral small-molecule drugs,” the guideline panelists wrote on the AGA website. “However, most of the evidence base is primarily derived from retrospective observational studies or comparisons of small cohorts. Data on patients’ values and preferences for specific management decisions and treatment choices are also limited. This results in substantial practice variability.”

Still, the area is advancing. Dr. Barnes and colleagues highlighted new scoring systems for

characterizing endoscopic findings and patient-reported outcomes, as well as the recent EARNEST trial (*N Engl J Med.* 2023 Mar 30;388[13]:1191-1200), which compared vedolizumab with placebo in patients with chronic refractory pouchitis, and should be considered a “landmark study in the field,” as it could shape future trial design.

Based on all available evidence and clinical experience, the panelists issued the following recommendations, which were approved by the AGA Governing Board.

Probiotics

Because of a knowledge gap, the guideline makes no recommendation for or against use of probiotics for either the primary prevention or treatment of pouchitis.

They offered a similar explanation for the lack of guidance on using probiotics to treat pouchitis, and noted that antibiotics have demonstrated effectiveness where probiotics have not, making them the preferred treatment choice.

“There is potential that delaying therapy or using probiotics when they are not as effective as antibiotics may have significant impact on an individual patient’s quality of life,” Dr. Barnes and colleagues noted.

In contrast with the above statements, the guideline recommends usage of probiotics to prevent recurrent pouchitis in patients with recurrent, antibiotic-responsive pouchitis.

The De Simone formulation of multistrain probiotics is best supported in this scenario, the

guideline notes, as this product was used in clinical trials, which collectively showed an 87% reduced risk of relapse over 12 months.

Antibiotics

Although the guideline supports antibiotics for prevention of pouchitis, the panelists noted that only one randomized controlled trial supports this recommendation, and negative effects of long-term usage need to be considered, including promotion of drug-resistant organisms and risk of *Clostridioides difficile* infection.

Dr. Barnes and colleagues cited more data supporting antibiotics for treatment of pouchitis, and noted that metronidazole and/or ciprofloxacin remain the preferred choices, with a typical duration of 2-4 weeks.

“An approach using a combination of antibiotics may be more effective in patients who do not respond to single-antibiotic therapy,” the panelists wrote, noting that oral vancomycin may also be considered when a patient does not respond to initial therapy.

For patients with recurrent pouchitis that relapses shortly after discontinuing antibiotics, chronic antibiotics should be considered, according to the guideline.

Immunosuppressive therapies

Advanced immunosuppressive therapies are recommended for patients with chronic antibiotic-dependent pouchitis, including those approved for treatment of UC or Crohn’s disease.

“Advanced immunosuppressive therapies may be used in lieu of chronic, continuous antibiotic therapy, particularly in patients who are intolerant to antibiotics or where patients and/or providers are concerned about risks of long-term antibiotic therapy,” the panelists wrote.

For patients with chronic antibiotic-refractory pouchitis, the guideline makes a general recommendation for advanced immunosuppressive therapies while specifically noting that vedolizumab has a greater strength of evidence in this scenario, citing the EARNEST trial.

A separate recommendation for corticosteroids is made for the same patient group, with ileal-release budesonide remaining the preferred formulation. In contrast, mesalamine is not recommended, based on a lack of supporting evidence.

The panelists recommend using corticosteroids in patients with Crohn’s-like disease of the pouch, and in patients with UC who have undergone IPAA and develop symptoms due to Crohn’s-like disease of the pouch, advanced immunosuppressive therapies approved for treatment of UC or CD may be used.

Finally, for patients with cuffitis, the guideline suggests using therapies that have been approved for the treatment of UC, including topical therapies (mesalamine and corticosteroids).

Future directions

“Even though pouchitis is relatively common after IPAA for UC, we

Continued on following page

Continued from previous page

mechanisms that mediate CMC sensitivity,” the investigators wrote.

To learn more, Dr. Daniel and colleagues conducted the present study, which involved a series of analyses and experiments.

They first compared inflammatory bowel disease-associated mutations and basal gene expression between CMC-sensitive and CMC-insensitive individuals from their previous trial. Neither were associated with CMC sensitivity, they found.

Evaluating microbiota was a more fruitful approach. Microbiome multivariable association with linear models analysis revealed 11 amplicon sequence variants (ASVs) that differed between groups.

“This algorithm did not detect differences between randomly selected subjects, arguing that ASVs that are associated with CMC sensitivity were not false discoveries but rather had marked, and perhaps contributed to, CMC

sensitivity status,” the investigators wrote.

Next, they transplanted pre-CMC fecal samples from two CMC-sensitive and two CMC-insensitive individuals into germ-free, colitis-prone, interleukin 10-/- mice. Exposing these mice to CMC led to distinct changes in microbiota that was not clearly associated with the sensitivity status of the donor. However, mice that received transplants from CMC-sensitive individuals demonstrated increased microbiota-derived proinflammatory markers, increased microbiota encroachment, and “stark” intestinal inflammation after CMC consumption, suggesting that these responses were somehow mediated by the microbiome.

“These [results] indicate a role for basal microbiotas in influencing CMC impact on this cardinal feature of intestinal inflammation and suspected driver of chronic diseases,” the investigators wrote.

“Our findings suggest that the microbiota participate in the extent to which an individual harbors proneness to CMC-induced inflammatory

diseases,” they added. “Accordingly, CMC consumption may be one trigger of chronic inflammation in genetically prone individuals colonized with a given microbial ecosystem.”

Research on a larger number of participants appears needed to substantiate their observations and determine the exact microbiota contributor(s) driving CMC sensitivity, the researchers concluded.

The investigators disclosed no conflicts of interest. Funding support came from a starting grant from the European Research Council under the European Union’s Horizon 2020 research and innovation program, a Chaire d’Excellence from IdEx Université de Paris, an award from the Fondation de l’Avenir, ANR grants EMULBIONT and DREAM, and the national program Microbiote from INSERM (B.C.). Support also came from National Institutes of Health grants, the Penn Center for Nutritional Science and Medicine, and the Max Planck Society. ■

More Comprehensive Testing Is Needed to Characterize Esophageal Dysphagia

BY WILL PASS

MDedge News

FROM GASTRO HEP ADVANCES

The current approach to esophageal function testing is insufficient to characterize esophageal motility disorders, as many patients with esophageal dysphagia have abnormalities that are undetectable with routine tests, according to investigators.

More nuanced assessments of esophageal motility disorders could potentially lead to more accurate diagnoses, and more effective treatments, reported Ravinder K. Mittal, MD, AGAF, and Ali Zifan, PhD, of the University of California San Diego.



Dr. Mittal

Esophageal motility disorders are currently divided into major and minor variants based on the contraction phase of peristalsis, Dr. Mittal and Dr. Zifan wrote in their report in *Gastro Hep Advances* (2023 Oct 5. doi: 10.1016/j.gastha.2023.08.021). Yet the reason for dysphagia in many of these patients remains a puzzle, particularly

in patients with supernormal contraction during peristalsis, like those with nutcracker esophagus. What's more, up to half of patients with dysphagia have normal findings on high-resolution manometry impedance (HRMZ), the typical diagnostic modality, leaving many with the broad label of functional dysphagia.

This lack of clarity "suggests that the etiology in many patients remains unknown," according to the investigators, which prompted them to publish the present review article.

After describing the shortcomings of current test methods, the investigators provided an overview of the physiology of esophageal peristalsis, then dove deeper into available data concerning luminal cross-section measurements, esophageal distension during peristalsis, bolus flow, and distension contraction patterns in normal patients versus those with various kinds of dysphagia.

They highlighted two key findings.

First, in patients with functional dysphagia, esophagogastric junction outflow obstruction (EGJO), and high-amplitude esophageal peristaltic contractions (HAEC), the bolus must travel through a narrow esophageal lumen. Second, in patients with nonobstructive dysphagia and type 3 achalasia, the bolus moves against distal luminal occlusion.

Medicine is strewn with diseases first labeled as functional or psychologically induced that have been recategorized into clear nonsensory disorders of which functional dysphagia is one.

In this review article, Dr. Mittal and Dr. Zifan discuss a summary and new paradigm for esophageal motility disorders and the origin of functional dysphagia (FD). As with other functional disorders, the predominance of research has suggested that functional dysphagia is in large part a sensory disorder in which patient are sensing normally subthreshold events of normal bolus transit interpreted as dysphagia.

In this review, largely a summary of Dr. Mittal's work, the role of more subtle characteristics of esophageal motility are examined. Several novel findings are observed including the role of increased esophageal wall tension and failure of relaxation with luminal narrowing as a cause of dysphagia. This may be due to inhibition or impaired relaxation or dyscoordination of the circular and longitudinal muscle layers during peristalsis. These novel findings are reinforced by a multidisciplinary approach blending the pressure findings on

high-resolution manometry, the motor and distensibility data from impedance planimetry (EndoFLIP), the anatomic findings of endoscopic ultrasound, and the bolus and anatomic information from barium esophagography, providing as complete a picture as possible for understanding dysphagia.

Will this lead to recategorization of all functional dysphagia as a perturbation in motor function and the discovery of new therapies? Certainly, to some degree, though sensory dysfunction will likely remain a prominent mechanism in some patients.

Nevertheless, it is always exciting when a new approach to an old disorder emerges. With the work from Dr. Mittal's laboratory and many others, functional dysphagia may soon drop the functional!

David A. Katzka, MD, is a gastroenterologist at New York-Presbyterian/Columbia University Irving Medical Center, New York, where he leads the Esophagology and Swallowing Center. He is an associate editor for *GI & Hepatology News*. He has performed research for Medtronic, but has no other relevant disclosures.



Dr. Katzka

"These findings indicate a relative dynamic obstruction to bolus flow and reduced distensibility of the esophageal wall in patients with several primary esophageal motility disorders," the investigators wrote. "We speculate that the dysphagia sensation experienced by many patients may result from a normal or supernormal contraction wave pushing the bolus against resistance."

Yet routine esophageal function testing fails to capture these abnormalities, Dr. Mittal and Dr. Zifan noted.

"[C]urrent techniques used to measure esophageal distension during peristalsis are not adequate," they wrote. "The high-resolution manometry and current scheme of classifying esophageal motor disorders in the current format emphasize only half of the story of peristalsis, probably the less important of the two halves, i.e., the contraction phase of peristalsis."

More focus is needed on esophageal distension, they suggested, noting that relaxation is first needed to accommodate a bolus before contraction, no matter how powerful, can push it down the esophagus.

"A simple analogy is that of a car — it cannot

get through a roadway that is smaller than its own width, irrespective of the horsepower of its engine," they wrote.

The solution may lie in a more comprehensive approach to esophageal function testing.

"Integrating representations of distension and contraction, along with objective assessments of flow timing and distensibility, complements the current classification of esophageal motility disorders that are based on the contraction characteristics," the investigators wrote, predicting that these efforts could improve diagnostic accuracy.

What to do about those diagnoses is another mystery.

"The question though remains regarding the optimal treatment for the impaired distension function of the esophagus, and whether improvement in the distension function will lead to improvement in dysphagia symptoms," the investigators concluded.

The review was supported by the National Institutes of Health. The investigators reported copyright/patent protection for the computer software (Dplots) used to evaluate the distension contraction plots. ■

Continued from previous page

observed that most of the evidence informing these guidelines was low to very low quality, derived from case series or small cohort studies, and several knowledge gaps exist,"

Dr. Barnes and colleagues wrote. "Several initiatives towards improving management of inflammatory pouch disorders are already underway. However, concerted efforts in key domains are central towards

improving patient care."

They suggested that research should focus on standardizing disease entities, characterizing natural history and risk factors for inflammatory disorders of the pouch, and

improving clinical trial design.

The guideline was funded by the AGA Institute. The panelists disclosed relationships with Bristol-Myers Squibb, Sandoz, AbbVie, and others. ■

MEMBER SPOTLIGHT

Dr. Rajeev Jain

Advocate from page 1

making the maintenance of certification (MOC) process more accessible and less burdensome.

People spent a lot of time studying for ABIM's 10-year MOC exam, sometimes even taking a course to help them pass. Now, there's an option in all specialties to take a 30-question exam every quarter.

On average, it takes someone roughly 2 minutes to answer each question on this short exam. "Per quarter, you're roughly spending an hour to do that instead of taking a big 10-year exam, where people were spending money and missing work," said Dr. Jain. This modality enables physicians to meet credentialing requirements "in a way that it meets many of the desires of our practitioners," he added.

Dr. Jain expounded on his work to advocate for patients and physicians in an interview.

Q: I'd like to discuss your opinion piece on UnitedHealthcare's advanced notification process. Did your article lead to any changes?

Dr. Jain: There's not a metric I can use to measure its success. But I

will tell you this: I've had numerous patients mention to me, "Hey, I saw your article in the *Dallas Morning News*. That was great." And that would lead to a conversation.

Q: Why do you think UHC's policy was a tool for prior authorization?

Dr. Jain: UHC has said as much – advance notification lays the groundwork for the GI endoscopy prior authorization program that United plans to roll out in "early 2024." Imagine you go to see a gastroenterologist in clinic, and the GI believes you need a procedure for certain symptoms or abnormal laboratory tests or imaging. It's not a screening procedure. It's a diagnostic procedure. Now, the insurance company is going to say, "Well, we can't schedule that until you do a preauthorization."

That could take a day. It could take a week. It could take longer. And now, the patient has lost that moment where they can get this settled. It's not just the schedule for the patient. They're going to get anesthesia, be it conscious sedation or deeper sedation, and they're going to need a ride home. They have to coordinate things with family members or friends. Those little logistics add up to a lot of times why patients cancel or don't show up or don't

Lightning Round

Favorite type of music?

1980s alternative

Favorite movie genre? Comedy

Cat person or dog person? Dog

Favorite sport? College football

What song do you have to sing along with when you hear it?

I Ran, by Flock of Seagulls

follow through, because we couldn't get it scheduled at that moment.

I feel like we are trying to attack this problem from many different angles, and my opinion piece was one of those tactics. The patients and the rank-and-file gastroenterologists appreciate the AGA being at the forefront of this issue.

Q: Your interests range from colon cancer to Barrett's esophagus and inflammatory bowel disease (IBD). Is there an area of focus you feel passionate about?

Dr. Jain: Through AGA, I was the cochair of the IBD Parenthood Project, which convened subject-matter

experts outside of GI, including maternal-fetal medicine, lactation experts, and patients. We came up with a care pathway for women in their reproductive years who have inflammatory bowel disease, including how they should think about family planning and what they should do during pregnancy and then the post partum. Those kinds of things have really kept me energized. It's sort of an antidote to burnout.

Q: Who are your mentors?

Dr. Jain: I would say the late Dan Foster, MD, who was the chair of medicine at UT Southwestern, and Mark Feldman, MD, AGAF, who held leadership roles at the Dallas VA Medical Center and then Texas Health Dallas. He retired a few years ago. They both expected physicians to understand the knowledge of how we were taking care of the patient and our professionalism. There's also my senior partner, Peter Loeb, MD, AGAF, who's now retired. He had an insatiable appetite for knowledge. Every time I'd come back from a meeting, he'd say, "Rajeev, tell me three things you learned." He always kept patients as the primary North Star; that whatever we did, we were thinking, "Is it best for the patient?" ■



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FND23-020

Recurrent Bleeding in Small-Intestinal Angiodysplasia Reduced by Thalidomide

BY WALTER ALEXANDER

In patients with recurrent bleeding due to small-intestinal angiodysplasia (SIA), treatment with thalidomide resulted in a reduction in bleeding, according to results of a new placebo-controlled trial.

At 1 year follow-up, thalidomide doses of 100 mg/day and 50 mg/day outperformed placebo in reducing by at least 50% the number of bleeding episodes, compared with the year prior to treatment, according to the study published online in the *New England Journal of Medicine* (2023 Nov 2. doi: 10.1056/NEJMoa2303706).

SIA, an increasingly recognized cause of repeat obscure gastrointestinal bleeding and iron-deficiency anemia, is a distinct vascular abnormality in the mucosa and submucosa characterized by focal accumulation of ectatic vessels. It is the most common cause of small-intestine bleeding, especially among patients older than 50.

There is a high unmet need among patients with SIA for an effective and relatively safe oral medication, given substantial recurrent bleeding risks following endoscopic or surgical procedures, and only observational studies suggest treatment with somatostatin and octreotide, noted senior author Zhizheng Ge, MD, Shanghai Jiao Tong University, Shanghai, China.

SIA is characterized by dilated and tortuous arterial or venous capillaries between thin-walled and immature veins and capillaries without a smooth-muscle layer. Its pathologic process involves chronic hypoxia and vessel sprouting.

Dr. Ge and colleagues postulated that thalidomide's ability to decrease the expression of proangiogenic factors and angiogenesis would have a long-lasting ameliorating effect on bleeding episodes of angiodysplasia, and thus a continued benefit with respect to bleeding cessation. Their previous small, single-center, open-label, randomized controlled trial of thalidomide for SIA showed a benefit, but it required larger confirmatory trials.

For their current trial, the researchers explored whether a short treatment period, selected to avoid

treatment nonadherence, could have a long-term effect. They randomly assigned on a 1:1:1 basis 150 patients with recurrent SIA-related bleeding, defined as at least four episodes during the previous year, to an oral daily dose of 100 mg of



Dr. Laine

thalidomide, 50 mg of thalidomide, or placebo for 4 months.

The patients (median age, 62.2 years; 88% aged 50 years or older) were followed for at least 1 year after treatment. The trial was conducted at 10 sites in China.

The primary endpoint was effective response, defined as a reduction of at least 50% in the number of bleeding episodes in the year following thalidomide treatment, compared with the number in the year before treatment. Bleeding was defined as the presence of overt bleeding or a positive fecal occult blood test.

The percentages of patients with effective response at 1-year follow-up were 68.6% in the 100-mg thalidomide group, 51% in the 50-mg thalidomide group, and 16% in the placebo group.

Among secondary endpoints, the incidence of rebleeding during the 4-month treatment period was 27.5% (14 of 51 patients) in the 100-mg thalidomide group, 42.9% (21 of 49 patients) in the 50-mg thalidomide group, and 90% (45 of 50 patients) in the placebo group. The percentage of patients who received a blood transfusion during the 1-year follow-up period were 17.6% in the 100-mg thalidomide group, 24.5% in the 50-mg thalidomide group, and 62% in the placebo group.

Cessation of bleeding, defined by two consecutive negative fecal occult blood tests on different days, during 1 year of follow-up was observed in 44 patients: 26 (51%) of patients in the 100-mg thalidomide group, 16 (32.7%) in the 50-mg

thalidomide group, and 2 (4%) in the placebo group. The authors urge further exploration of the duration of benefit and the efficacy of longer courses of treatment.

Adverse events, all grade 1 or 2, resolved after treatment of symp-

While thalidomide effectively prevented rebleeding for 42 patients during the year after therapy was stopped, suggesting an alteration of angiodysplasias, rebleeding during the subsequent 3-27 months occurred among 20 of those patients. "That finding suggests that retreatment will be needed."

toms, completion of treatment, or discontinuation of thalidomide or placebo.

Retreatment May Be Necessary

In an accompanying editorial, Loren Laine, MD, AGAF, chief of the section of digestive diseases, internal medicine, and medical chief, digestive health, Yale School of Medicine, New Haven, Connecticut, affirmed the authors' conclusions and commended the quality of evidence they provided.

"Their results suggest that thalidomide may be disease-modifying, with efficacy persisting after discontinuation," wrote Dr. Laine, also a Yale professor of medicine and digestive diseases.

While thalidomide effectively prevented rebleeding for 42 patients during the year after therapy was stopped, suggesting an alteration of angiodysplasias, rebleeding during the subsequent 3-27 months occurred among 20 of those patients, Dr. Laine noted. That finding "suggests that retreatment will be

needed," although the appropriate duration of treatment before retreatment and the duration of retreatment remain unclear, he added.

The study's reliance on bleeding episodes that were defined by positive fecal occult blood tests, which may be clinically unimportant, is a weakness in the trial, Dr. Laine wrote.

Despite the study's positive findings, clinicians may still prefer somatostatin analogues because of their potential for better safety and, with once-monthly injections versus daily thalidomide pills, their likelihood for better adherence, Dr. Laine wrote. "[They] will reserve thalidomide for use in patients who have continued bleeding or side effects with somatostatin analogues," he added.

Somatostatin is rarely used in the treatment of SIA bleeding in China, where thalidomide is relatively easy to obtain and is being used clinically, Dr. Ge told this news organization in response to Dr. Laine's editorial. "The clinical application of thalidomide has been taken up in other [Chinese] hospitals that have seen our research," he added.

Future research may include randomized controlled trials of somatostatin, since Chinese experience with it is so limited, Dr. Ge said. "We would want to compare efficacy, safety, feasibility, and cost-effectiveness between somatostatin and thalidomide," he added.

The study was supported by grants from the National Natural Science Foundation of China and a grant from the Shanghai Municipal Education Commission, Gaofeng Clinical Medicine. The author disclosures can be found with the original article. ■

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Is AI Inevitable?

Colonoscopy from page 1

detection (CAdE) system at a single academic center in Chicago found that for screening and surveillance colonoscopy combined, endoscopists using CAdE identified more adenomas and serrated polyps — but only endoscopists who used CAdE regularly (“majority” users).

A systematic review and meta-analysis of 21 randomized controlled trials (*Ann Intern Med.* 2023 Aug. doi: 10.7326/M22-3678) comparing CAdE with standard colonoscopy found increased detection of adenomas, but not of advanced adenomas, as well as higher rates of unnecessary removal of nonneoplastic polyps.

Adding to the mix, a multicenter randomized controlled trial of patients with a positive fecal immunochemical test found that AI use was not associated with better detection of advanced neoplasias. Lead author Carolina Mangas Sanjuán, MD, PhD, Hospital General Universitario Dr. Balmis, Alicante, Spain, told this news organization the results were “surprising,” given previous studies showing benefit.

Similarly, a pragmatic implementation trial (*Gastroenterology.* 2022 Dec. doi: 10.1053/j.gastro.2022.12.004) conducted by Stanford, California, researchers showed no significant effect of CAdE on ADR, adenomas per colonoscopy, or any other detection metric. Furthermore, CAdE had no effect on procedure times or non-neoplastic detection rates.

The authors cautioned against viewing their study as an “outlier,” however, and pointed to an Israeli study (*Am J Gastroenterol.* 2022 Nov. doi: 10.14309/ajg.0000000000001970) comparing adenoma and polyp detection rates 6 months before and after the introduction of AI-aided colonoscopy. Those authors reported no performance improvement with the AI device and concluded that it was not useful in routine practice.

A ‘Mishmash’ of Methods

“It’s not clear why some studies are positive, and some are negative,” Dr. Sharma acknowledged.

Study design is a factor, particularly in real-world studies, he said. Some researchers use the before/after approach, as in the Israeli study; others compare use in different rooms — that is, one with a CAdE device and one without. Like the Chicago analysis, findings from such studies probably depend on whether the colonoscopists with the CAdE device in the room actually use it.

Other real-world studies look at detection by time, Dr. Sharma said.

For example, a study of 1780 colonoscopies in China (*JAMA Netw Open.* 2023 Jan. doi: 10.1001/jamanetworkopen.2022.53840) found that AI systems showed higher assistance ability among colonoscopies performed later in the day, when adenoma detection rates typically declined, perhaps owing to fatigue.

These authors suggest that AI may have the potential to maintain high quality and

homogeneity of colonoscopies and improve endoscopist performance in large screening programs and centers with high workloads.

“There’s a mishmash of different kinds of real-world studies coming in, and it’s very difficult to figure it all out,” Dr. Sharma said. “We just have to look at these devices as innovations and embrace them and work with them to see how it fits in our practice.”

Perceptions and Expectations

Emerging evidence suggests that endoscopists’ perceptions and expectations may affect assessments of AI’s potential benefits in practice, Dr. Sharma noted.

“Someone might say, ‘I’m a trained physician. Why do I need a machine to help me?’ That can create a situation in which the endoscopist is constantly challenging the device, trying to overrule it or not give it credit.”

Others might perceive that the AI device will definitely help and therefore not look as carefully themselves for adenomas.

A study at the University of Texas MD Anderson Cancer Center in Houston (*Gastrointest Endosc.* 2023 Jul. doi: 10.1016/j.gie.2023.02.016) in which activation of the AI system was at the discretion of the endoscopist found that real-time CAdE did not improve adenoma detection among endoscopists with high baseline detection rates.

However, despite its availability, AI-assisted colonoscopy was activated in only half of the cases, and multiple concerns were raised by staff and endoscopists in a postprocedural survey. In particular, endoscopists were concerned that the system would result in too many false-positive signals (82.4%), was too distracting (58.8%), and prolonged procedure time (47.1%).

The authors of the Stanford study that found no benefit with CAdE in routine practice noted, “Most concerning would be if, inadvertently, CAdE use was accompanied by a simultaneous unconscious degradation in the quality of mucosal exposure, possibly due to a false sense of comfort that CAdE would ensure a high-quality examination.”

“We’re trying to evaluate some of these interactions between endoscopists and AI devices both pragmatically in practice as well as in clinical trials,” Dr. Sharma said. “Much depends on the context of how you approach and present the devices. We tell physicians that this is an assist device, not something you’re competing against and not something that’s here to replace you. This is something which may make your lives easier, so try it out.”

Are Less Experienced Endoscopists Helped More?

It seems intuitive that less experienced endoscopists would be helped by AI, and indeed, some recent studies confirm this.

A small randomized controlled trial in Japan (*Gastrointest Endosc.* 2023 Jun. doi: 10.1016/j.gie.2023.04.1164), presented during the Presidential Plenary at the American Society for Gastrointestinal Endoscopy (ASGE) annual meeting in May 2023, showed that a CAdE system was “particularly useful” for beginning endoscopists, who had lower adenoma miss rates with the

device vs a white-light control device.

Another randomized controlled trial in Japan (*Clin Gastroenterol Hepatol.* 2023 Oct. doi: 10.1016/j.cgh.2023.10.019) found that CAdE use was associated with an increased overall ADR among endoscopists in training.

But experienced endoscopists probably can benefit as well, noted Jennifer Christie, MD, AGAF, Division Director, Gastroenterology and Hepatology at the University of Colorado School of Medicine Anschutz Medical Campus in Aurora.

“We know that these AI devices can be useful in training our fellows to detect certain lesions in the colon,” she said. “However, they’re also helpful for many very seasoned practitioners, as an adjunctive tool to help in terms of diagnosis.”

Some studies reflect that dual benefit.

The AID-2 study, designed specifically to look at whether experience had an effect on AI findings during colonoscopy (*Gut.* 2021 Jun. doi: 10.1136/gutjnl-2021-324471), was conducted among nonexpert endoscopists (lifetime volume of less than 2000 colonoscopies). The researchers, including Dr. Sharma, found that CAdE increased the ADR by 22% compared with the control group.

An earlier study, AID-1, used a similar design but was conducted among experienced endoscopists (*Gastroenterology.* 2020 May. doi: 10.1053/j.gastro.2020.04.062). In AID-1, the ADR was also significantly higher in the CAdE group (54.8%) compared with the control group (40.4%), and adenomas detected per colonoscopy were significantly higher in the CAdE group (mean, 1.07) than in the control group (mean, 0.71).

A multivariate post hoc analysis that pooled results from both AID-1 and AID-2 (*Gut.* 2022 Apr. doi: 10.1136/gutjnl-2021-324471) showed that use of CAdE and colonoscopy indication, but not the level of examiner experience, were associated with ADR differences. This led the researchers to conclude, “Experience appears to play a minor role as a determining factor for ADR.”

Similarly, a 2023 study from China (*Clin Gastroenterol Hepatol.* 2022 Jul. doi: 10.1016/j.cgh.2022.07.006) looked at the mean number of adenomas detected per colonoscopy according to the endoscopist’s experience. All rates were significantly higher in AI-assisted colonoscopies compared with conventional non-AI colonoscopy: overall ADR, 39.9% vs 32.4%; advanced ADR, 6.6% vs 4.9%; ADR of expert endoscopists, 42.3% vs 32.8%; ADR of nonexpert endoscopists, 37.5% vs 32.1%; and adenomas per colonoscopy, 0.59 vs 0.45, respectively.

The authors concluded that “AI-assisted colonoscopy improved overall ADR, advanced ADR, and ADR of both expert and nonexpert attending endoscopists.”

Improving the Algorithms

Experts agree that current and future research will improve the accuracy and quality of AI colonoscopy for all users, leading to new standards

Continued on following page



Dr. Sharma



Dr. Christie

AI Shows Potential for Detecting Mucosal Healing in Ulcerative Colitis

BY CAROLYN CRIST

FROM DIGESTIVE AND LIVER DISEASE

Artificial intelligence (AI) systems show high potential for detecting mucosal healing in ulcerative colitis with optimal diagnostic performance, according to a new systematic review and meta-analysis.

AI algorithms replicated expert opinion with high sensitivity and specificity when evaluating images and videos. At the same time, moderate-high heterogeneity of the data was found, the authors noted.

“Artificial intelligence software is expected to potentially solve the longstanding issue of low-to-moderate interobserver agreement when human endoscopists are required to indicate mucosal healing or different grades of inflammation in ulcerative colitis,” Alessandro Rimondi, lead author and clinical fellow at the Royal Free Hospital and University College London Institute for Liver and Digestive Health, London, England, told this news organization.

“However, high levels of heterogeneity have been found, potentially linked to how differently the AI software was trained and how many cases it has been tested on,” he said. “This partially limits the quality of the body of evidence.”

The study was published online in *Digestive and Liver Disease* (2023 Dec 5. doi: 10.1016/j.dld.2023.11.005).

Evaluating AI Detection

In clinical practice, assessing mucosal healing in inflammatory bowel disease (IBD) is critical for

evaluating a patient’s response to therapy and guiding strategies for treatment, surgery, and endoscopic surveillance. In an era of precision medicine, assessment of mucosal healing should be precise, readily available in an endoscopic report, and highly reproducible, which requires high accuracy and agreement in endoscopic diagnosis, the authors noted.

“We probably need a consensus or guidelines that identify the standards for training and testing newly developed software, stating the bare minimum number of images or videos.”

AI systems — particularly deep learning algorithms based on convolutional neural network architecture — may allow endoscopists to establish an objective and real-time diagnosis of mucosal healing and improve the average quality standards at primary and tertiary care centers, the authors wrote. Research on AI in IBD has looked at potential implications for endoscopy and clinical management, which opens new areas to explore.

Dr. Rimondi and colleagues conducted a systematic review of studies up to December 2022 that involved an AI-based system used to estimate any degree of endoscopic inflammation in IBD, whether ulcerative colitis or Crohn’s disease. After that, they conducted a diagnostic test accuracy meta-analysis restricted to the field in which more

than five studies providing diagnostic performance — mucosal healing in ulcerative colitis based on luminal imaging — were available.

The researchers identified 12 studies with luminal imaging in patients with ulcerative colitis. Four evaluated the performance of AI systems on videos, six focused on fixed images, and two looked at both.

Overall, the AI systems achieved a satisfactory performance in evaluating mucosal healing in ulcerative colitis. When evaluating fixed images, the algorithms achieved a sensitivity of 0.91 and specificity of 0.89, with a diagnostic odds ratio (DOR) of 92.42, summary receiver operating characteristic curve (SROC) of 0.957, and area under the curve (AUC) of 0.957. When evaluating videos, the algorithms achieved 0.86 sensitivity, 0.91 specificity, 70.86 DOR, 0.941 SROC, and 0.941 AUC.

“It is exciting to see artificial intelligence expand and be effective for conditions beyond colon polyps,” Seth Gross, MD, AGAF, professor of medicine and clinical chief of gastroenterology and hepatology at NYU Langone Health, New York, told this news organization.

Dr. Gross, who wasn’t involved with this study, has researched AI applications in endoscopy and colonoscopy. He and colleagues have found that machine learning software can improve lesion and polyp detection, serving as a “second set of eyes” for practitioners.

“Mucosal healing interpretation can be variable amongst providers,” he said. “AI has the potential to help standardize the assessment of mucosal healing in patients with ulcerative colitis.”

Improving AI Training

The authors found moderate-high levels of heterogeneity among the studies, which limited the quality of the evidence. Only 2 of the 12 studies used an external dataset to validate the AI systems, and 1 evaluated the AI system on a mixed database. However, seven used an internal validation dataset separate from the training dataset.

It is crucial to find a shared consensus on training for AI models, with a shared definition of mucosal healing and cutoff thresholds based on recent guidelines, the authors noted. Training data should be on the basis of a broad and shared database containing images and videos with high interobserver agreement on the degree of inflammation.

“We probably need a consensus or guidelines that identify the standards for training and testing newly developed software, stating the bare minimum number of images or videos for the training and testing sections,” Dr. Rimondi said.

In addition, due to interobserver misalignment, an expert-validated database could help serve the purpose of a gold standard, he added.

“In my opinion, AI tends to better perform when it is required to evaluate a dichotomic outcome (such as polyp detection, which is a yes or no task) than when it is required to replicate more difficult tasks (such as polyp characterization or judging a degree of inflammation), which have a continuous range of expression,” Dr. Rimondi said.

The authors declared no financial support for this study. Dr. Rimondi and Dr. Gross reported no financial disclosures. ■

Continued from previous page

and more consistent outcomes in both clinical trials and real-world applications.

Work underway now to improve the algorithms will be an important step in that direction, according to Dr. Christie.

“We need to have enough information to create AI algorithms that allow us to detect early lesions, at least from an imaging standpoint, and we need to improve and increase the sensitivity and the specificity, as well as the predictive value,” she said.

AI can also play a role in health equity, she noted.

“But it’s a double-edged sword, because it depends again on algorithms and machine learning. Perhaps AI can eliminate some of the bias

in our clinical decision-making. However, if we don’t train the machine properly with a good, diverse sample of patients and figure out how to integrate some of the social determinants of health that a computer may not otherwise consider, it can create larger disparities and larger biases. AI devices can only be as good and as inclusive as we make them,” Dr. Christie said.

Looking Ahead

Dr. Sharma predicts that “the next slew of studies are going to be on characterization — not just saying there’s an abnormality but distinguishing it further and saying whether the lesion is noncancerous, precancerous, or cancer.”

Other studies will focus on quality

improvement of factors, such as withdrawal time and bowel preparation.

In its clinical practice update on AI (*Gastroenterology*. 2023 Oct. doi: 10.1053/j.gastro.2023.07.010), the American Gastroenterological Association states, “Eventually, we predict an AI suite of tools for colonoscopy will seem indispensable, as a powerful adjunct to support safe and efficient clinical practice. AI tools that improve colonoscopy quality may become more accepted, and perhaps demanded, by payors, administrators, and possibly even by well-informed patients who want to ensure the highest-quality examination of their colon.”

Dr. Sharma and Dr. Christie disclose no relevant conflicts of interest. ■

Is There a Safe Alcohol Limit in Early Liver Disease?

BY MEGAN BROOKS

Daily consumption of up to half of a standard US drink (7.4 gram/day) does not appear to increase mortality risk in adults with steatotic liver disease (SLD) who have low risk for advanced fibrosis.

Researchers at Cedars-Sinai Medical Center, Los Angeles, California, used data from the National Health and Nutrition Examination Survey III (1988-1994) to elucidate the dose-dependent association of alcohol use with SLD progression.



Dr. Yeo

The results of the study were published in an online-first research letter in *JAMA Network Open* (2023 Dec. doi: 10.1001/jamanetworkopen.2023.47548).

The coauthors, led by Yee Hui Yeo, MD, a gastroenterology/hepatology fellow at Cedars-Sinai, identified 2834 adults with confirmed SLD (51.8% male, 34.2% non-Hispanic White), including 591 (20.8%) with intermediate or high risk for advanced fibrosis, defined as a Fibrosis-4 index (FIB-4) score of 1.3 or higher.

Multivariable Cox regression with restricted cubic splines was used to investigate nonlinear associations between alcohol use and mortality.

During median follow-up of 26 years, the mortality rate per 100,000 persons was 4342 in the group with intermediate and high risk for advanced fibrosis versus 1099 in the low-risk group.

After adjustment for demographics and metabolic variables, there was a nonlinear association between alcohol intake and mortality in the low-risk group ($P = .001$ for nonlinearity). In this group, the mortality risk threshold was < 7.4 gram/day, which equals half a 12-ounce beer or half a glass of wine. Each additional gram above this level led to a higher death rate.

No safe alcohol limit was evident in the intermediate- and high-risk group; their mortality risk rose with any alcohol intake.

“Recent guidelines have recommended the FIB-4 score as a first-line assessment tool given its low cost, high accuracy, and

noninvasiveness,” the authors write. “In this study we proposed using the FIB-4 score to guide clinicians in advising patients with SLD who choose not to abstain

completely from alcohol.”

The study relied on self-reported alcohol intake and lacked data on drinking patterns. Individual risks may vary and require case-by-case

discussion as the data are population based.

Funding sources were not listed and the authors reported no conflicts of interest. ■

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Endoscopic Management of Benign Gallbladder Disease



BY ANDREW J. GILMAN, MD, AND
TODD H. BARON, MD

Introduction

The treatment of benign gallbladder disease has changed substantially in the past decade, but this represents only a snapshot in the evolutionary history of the management of this organ. What began as a problem managed exclusively by open cholecystectomy (CCY) transitioned into a race toward minimally invasive approaches in the 1980s, with advances from gastroenterology, surgery, and radiology.

The opening strides were made in 1980 with the first description of percutaneous cholecystostomy (PC) by Dr. R.W. Radder.¹ Shortly thereafter, in 1984, Dr. Richard A. Kozarek first reported the feasibility of selective cystic duct cannulation during endoscopic retrograde cholangiopancreatography (ERCP).² Subsequent stenting for the treatment of acute cholecystitis (endoscopic transpapillary gallbladder drainage, ET-GBD) was then reported by Tamada et. al. in 1991.³ Not to be outdone, the first laparoscopic cholecystectomy (LC) was completed by Dr. Med Erich Mühe of Germany in 1985.⁴ More recently, with the expansion of interventional endoscopic ultrasound (EUS), the first transmural EUS-guided gallbladder drainage (EUS-GBD) was described by Dr. Baron and Dr. Topazian in 2007.⁵

The subsequent advent of lumen apposing metal stents (LAMS) has cemented EUS-GBD in the toolbox of treatment for benign gallbladder disease. Results of a recent prospective multicenter trial, with a Food and Drug Administration (FDA)-approved protocol and investigational device exemption, have been published, opening the

door for the expansion of FDA-approved indications for this device.⁶

Benign gallbladder disease encompasses both polyps (benign and premalignant) and cholecystitis (acute/chronic, calculous/acalculous), in addition to others. The four management techniques (LC, PC, ET-GBD, and EUS-GBD) have filled integral niches in the management of these patients. Even gallbladder polyps have not been able to escape the reach of endoscopic approaches with the recent description of LAMS-assisted polypectomy as part of a gallbladder-preserving strategy.^{7,8} While EUS-GBD also has been used for biliary decompression in the presence of a patent cystic duct and absence of cholecystitis, this article will focus on ET-GBD and EUS-GBD for the primary treatment of cholecystitis or symptomatic cholelithiasis.⁹ Both of these techniques have gained wide recognition and/or guideline support for their use from the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE).^{10,11} In addition, there is now one FDA-approved stent device for treatment of acute cholecystitis in patients unfit for surgery.

Techniques & Tips

ET-GBD

- During ERCP, after successful cannulation of the bile duct, attempted wire cannulation of the cystic duct is performed.
 - A cholangiogram, which clearly delineates the insertion of the cystic duct into the main bile duct, can enhance cannulation success. Rotatable fluoroscopy can facilitate identification.
- After anatomy is clear, wire access is often best achieved using a



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sphincterotome or stone retrieval (occlusion) balloon.

- The balloon, once inflated, can be pulled downward to establish traction on the main bile duct, which can straighten the approach.
- After superficial wire engagement into the cystic duct, the accessory used can be slowly advanced into the cystic duct to stabilize the catheter and then navigate the valves of Heister to reach the gallbladder lumen.
 - Use of a sphincterotome, which directs toward the patient's right (most often direction of cystic duct takeoff), is helpful. Angled guidewires are preferable. We often use a 0.035-inch, 260-cm angled hydrophilic wire (GLIDEWIRE; Terumo, Somerset, NJ) to overcome this challenging portion of ET-GBD.
 - If despite the above maneuvers the guidewire has failed to enter the cystic duct, cholangioscopy can be used to identify the

orifice and/or stabilize deep wire cannulation. This is often cumbersome, is time consuming, does not always produce success, and requires additional expertise.

- If a stone is encountered that cannot be extracted or traversed by a guidewire, cholangioscopy with electrohydraulic lithotripsy can be pursued.
- After the guidewire has entered the gallbladder, a 5-French or 7-French plastic double-pigtail stent is placed. Typical lengths are 9-15 cm.
 - Some authors prefer to use two side-by-side plastic stents.¹² This has been shown retrospectively to enhance the long term clinical success of ET-GBD but with additional technical difficulty.
- This stent can remain in place indefinitely and need not be exchanged, though it should be removed just prior to CCY if pursued. Alternatively, the surgeon can be alerted to its presence and, if comfortable, it can be removed intraoperatively.

Endoscopic management of benign gallbladder disease, predominantly gallstone-related disease, has advanced significantly over the last decades to offer minimally invasive ways to treat patients who are not surgical candidates for cholecystectomy. These options include endoscopic transpapillary gallbladder drainage (ET-GBD) and endoscopic ultrasound-guided gallbladder drainage (EUS-GBD).

In this issue's "In Focus," Dr. Andrew J.

Gilman and Dr. Todd H. Baron present techniques and tips for successful ET-GBD and EUS-GBD procedures. They also review the current literature on adverse events and clinical outcomes of both techniques, which are important to discuss with patients when considering these endoscopic alternatives.

Judy A. Trieu, MD, MPH
Editor-in-Chief
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Dr. Trieu

EUS-GBD

- Use of fluoroscopy is optional but can enhance technical success in selected situations.
- Conversion, or internalization, of PC is reasonable and can enhance patient quality of life.¹³
- If the gallbladder wall is not in close apposition to the duodenal (or gastric) wall, consider measuring the distance.

- We preferentially use 10-mm diameter by 10-mm saddle length LAMS for EUS-GBD, unless the above distance warrants use of a 15-mm by 15-mm LAMS (AXIOS, Boston Scientific, Marlborough, MA). If the distance is greater than 15 mm, consider searching for an alternative site, using a traditional biliary fully covered self-expandable metal stent (FCSEMS) for longer length, or converting to ET-GBD. Smaller diameter (8 mm) with an 8-mm saddle length can be used as well. The optimal diameter is unknown and also dependent on whether transluminal endoscopic diagnosis or therapy is a consideration.
 - If there is difficulty locating the gallbladder, it may be decompressed or small (particularly if PC or a partial CCY has already been performed).
 - If a cholecystostomy tube is in place, instillation of sterile water via the tube can sometimes improve the target for LAMS placement, though caution should be made to not over-distend the gallbladder. ERCP with placement of a nasobiliary tube into the gallbladder can also serve this purpose and has been previously described.¹⁴
 - The gallbladder can be punctured with a 19-gauge FNA needle to instill sterile water and distend the gallbladder with the added benefit of being able to pass a guidewire, which may enhance procedural safety in difficult cases. However, success of this technique is contingent on fluid remaining within the gallbladder and not transiting out via the cystic duct. Expedient exchange of the FNA needle for the LAMS device may be necessary.
 - Attempt to confirm location within the duodenum prior to puncture, as gastric origins can pose unique ramifications (i.e., potential for partial gastric outlet obstruction, obstruction of LAMS with food debris, etc.).
 - It can be easy to mistake an unintentional prepyloric position for a position within the duodenum since the working channel is behind (proximal to) the echoprobe.
 - Turning off Doppler flow prior to advancement of the cautery enhanced LAMS can reduce obscurement of views on entry into the gallbladder. Lack of certainty about entry or misdeployment after presumed entry herald
- the most challenging aspect of EUS-GBD.
- Utilization of a previously placed guidewire or advancement of one preloaded into the LAMS can aid in both enhancing confidence in location and assist with salvage maneuvers, if needed.
 - After successful deployment of the LAMS we routinely place a double-pigtail plastic stent through it (typically 7 French by 4 cm) to maintain patency. This may also prevent bleeding from the LAMS flange abrading the wall of either lumen.
 - We routinely exchange the LAMS for two double-pigtail plastic stents (typically 7 French by 4 cm) 4 weeks after initial placement especially when there is a more than modest residual stone burden (data in press). These plastic stents can remain in place indefinitely.
 - This exchange can be deferred if the patient is not expected to survive until the 1-year anniversary of LAMS deployment. After 1 year the LAMS plastic covering may degrade and pose additional problems.¹⁵
- LAMS Misdeployment Salvage Tips**
- Salvage techniques can vary from simple to complex.
 - If a wire is in place, it can be used to balloon or catheter dilate the tract and place a FCSEMS traversing the gallbladder and duodenal/gastric lumens. A similar approach can be used if the LAMS deployed on only one side (gallbladder or duodenum/stomach) and the other flange is within the peritoneum.
 - The most challenging scenario to salvage is if the LAMS is misdeployed or becomes dislodged and no wire is present. This is why the use of a guidewire, even if preloaded into the LAMS and placement is freehand, is essential for EUS-GBD. A potential technique is to balloon dilate the duodenal/gastric defect and drive the endoscope into the peritoneum to reconnect that lumen to the gallbladder defect or LAMS, depending on the site of misdeployment. Doing so requires a high degree of commitment and skill and should not be done casually.
 - If uncertainty remains or if misdeployment has occurred and salvage attempts have failed, consider closure of the duodenal/gastric defect and conversion to ET-GBD.

- This may both treat the initial procedural indication and assist with what is essentially a large bile leak, which might also require percutaneous therapy for nonsurgical management.
- For endoscopists with limited experience at salvage techniques, it is reasonable for the threshold for conversion to be low, assuming experience with and confidence in ET-GBD are high.
- If salvage is successful but ambiguity remains, consider obtaining a cholangiogram via the LAMS to confirm positioning and absence of leak.

Adverse Events

Both ET-GBD and EUS-GBD should be performed by an endoscopist comfortable with their techniques and the management of their ad-

The decision on which technique to utilize for endoscopic management of cholecystitis or symptomatic cholelithiasis depends first and foremost on the expertise and comfort level of the endoscopist.

verse events (AEs). Rates for EUS-GBD AEs in patients at high risk for LC were reported in one international multicenter registry to be 15.3% with a 30-day mortality of 9.2%, with a significant predictor of AE being endoscopist experience less than 25 procedures.¹⁶ A meta-analysis also found an overall AE rate of 18.31%, with rates for perforation and stent related AEs (i.e. migration, occlusion, pneumoperitoneum) being 6.71% and 8.16%, respectively.¹⁷ For this reason, we recommend that patients with cholecystitis who are deemed to be poor surgical candidates be transferred to a tertiary referral center with expertise in these approaches. Rates of AEs for ET-GBD are similar to that for standard ERCP, with reported ranges of 5%-10.3%.¹⁰

Comparisons Between Techniques

The decision on which technique to utilize for endoscopic management of cholecystitis or symptomatic cholelithiasis depends first and foremost on the expertise and comfort level of the endoscopist. Given the additional training that an advanced endoscopist needs to perform EUS-GBD, combined with the perhaps

slightly higher AE rate and permanency of endoscopic cholecystostomy, it is reasonable to proceed with a trial of ET-GBD if confidence is insufficient. However, ET-GBD can certainly be more technically challenging and less effective than EUS-GBD, with lower reported technical and clinical success rates (technical 85.3% vs 93.0%, clinical 95.2% vs 97.3%).¹⁸ Despite this, the rate of recurrence of cholecystitis is similar between ET-GBD and EUS-GBD (4.6% vs 4.2%).¹⁹ As stated above in the Techniques & Tips section, some authors utilize two plastic stents for ET-GBD for this purpose, though with increased technical difficulty. It is important to remember that these numbers, when paired with AE rates, represent the achievements of expert endoscopists.

Discussion with your surgery team is important when deciding modality. If the patient is felt to be a potential candidate for CCY, and EUS-GBD is not being used as a destination therapy, the surgeon may prefer ET-GBD. EUS-GBD may enhance the difficulty of CCY, though at least one study demonstrated that this was no different than PC with similar rates of conversion from LC to open CCY.²⁰ This conversation is most critical for patients who are potential liver transplant candidates. For patients where this is not a consideration, there is some evidence to suggest equivalency between LC and EUS-GBD, though certainly EUS-GBD has not yet supplanted LC as the treatment of choice.²¹

While there may eventually be a shift toward EUS-GBD instead of LC in certain patient groups, what is clearer are the advantages of EUS-GBD over PC. One recent meta-analysis revealed that EUS-GBD has significantly favorable odds of overall adverse events (OR, 0.43; 95% CI, 0.18-1.00), shorter hospital stay (2.76 less days, 95% CI, 0.31-5.20 less days), reinterventions (OR, 0.15; 95% CI, 0.02-0.98), and unplanned readmissions (OR, 0.14; 95% CI, 0.03-0.70) compared to PC.²² Beyond the data, though, are the emotional and psychological impacts an external drain can have on a patient.

Conclusion

When expertise is available, endoscopic treatment of benign gallbladder disease has a definite role but should be undertaken only by those with the experience and skill to safely do so. Decision to proceed, especially with EUS-GBD, should be accompanied by conversation and

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Ozempic Is Appealing, but Not Cost-Effective, for Obesity Treatment

BY JOANNA BRODER

MDedge News

To lose weight, patients with obesity may be more interested in semaglutide products, but the glucagon-like peptide 1 agonists, such as Ozempic injections and Rybelsus tablets, are not yet cost-effective, according to a modeling study that compared the drugs with surgery and endoscopy.

Sleeve gastrectomy (SG) for moderate to severe (class II/III) obesity and the less invasive endoscopic sleeve gastroplasty (ESG) for mild (class I) obesity were both cost-effective strategies to reduce obesity, the researchers report.

“SG should be offered as the first-line treatment for class II and class III obesity,” write Monica Saumoy, MD, of the Center for Digestive Health, Penn Medicine Princeton Medical Center,

Plainsboro, New Jersey, and coauthors. “ESG is an effective and cost-effective nonsurgical treatment for class I, class II and class III obesity, and more efforts are needed to ensure that patients have access to this procedure.



Dr. Saumoy

“While semaglutide is highly effective for weight loss, and there is substantial patient interest, it is not currently cost-effective due to its high cost,” they add. “With methods to reduce semaglutide’s annual cost, it may provide an effective and cost-effective method

to reduce the morbidity related to obesity.”

The study was published in *Gut* (2023 Dec. doi: 10.1136/gutjnl-2023-330437).

Cost Concerns

One in two Americans will likely be obese by 2030, according to current models, and nearly one in four adults will be severely obese.

Several weight-loss therapies exist to treat obesity. Evidence shows bariatric surgery is effective in reducing weight, metabolic comorbidities, and mortality in people with obesity compared with lifestyle intervention alone, but surgery has risks, adverse events, and poor national uptake. Patients are likely more interested in less invasive options, the authors write.

Recent trials have reported effective weight loss from less invasive options. A 5-year follow-up of the randomized controlled MERIT trial found that ESG was associated with

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collaboration with surgical teams. If a patient is under consideration for PC instead of LC, it may be worthwhile to seek consultation with a local center with expertise in EUS-GBD or ET-GBD. The adoption of these techniques is part of the paradigm shift, seen broadly throughout medicine, towards minimally invasive interventions, particularly in advanced endoscopy. ■

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a 13.6% total body weight loss for people with mild to moderate obesity.

On the pharmaceutical front, other randomized controlled trials have shown that semaglutide is linked with as much as 17% total body weight loss at 2 years. Also, recent guidance from the American Gastroenterological Association (AGA) states that long-term treatment with a semaglutide is the preferred strategy for weight loss (*Gastroenterology*. 2022 Nov. doi: 10.1053/j.gastro.2022.08.045).

“However, concerns about the cost and the cost-effectiveness of these [less invasive] interventions have limited their usage in the USA,” the study authors write.

The aim of the study was to perform a cost-effectiveness analysis comparing SG, ESG, semaglutide, and lifestyle interventions (LI) for patients with obesity in class I (defined as body mass index 30-34.9 kg/m²), class II (35-29.9 kg/m²), and class III (>40kg/m²) obesity.

Researchers used a state-transition, semi-Markov microsimulation model to analyze the effectiveness of ESG, SG, semaglutide, and LI in a simulated 40-year-old with three different base-case scenarios of class I, II, or III obesity. They then performed a detailed threshold and sensitivity analysis to change the cost of treatment modalities and the semaglutide adherence rate. Outcome measures included a willingness-to-pay threshold of US \$100,000/quality-adjusted life years (QALY) and incremental cost-effectiveness ratios (ICERs).

Cost-Effectiveness

When the treatment modalities were compared with each other, findings showed that for class I obesity, ESG was cost-effective (US \$4,105/QALY). For class II and III obesity, SG was cost-effective as well (US \$5,883/QALY) and (US \$7,821/QALY), respectively.

In all classes of obesity, SG and ESG were cost-effective compared with LI. Semaglutide was not cost-effective compared with LI for class I, II, and III obesity (ICER US \$508,414/QALY, \$420,483/QALY, and \$350,637/QALY, respectively).

“For semaglutide to be cost-effective when compared with ESG, it would have to cost less than US \$1,879 (class III), US \$1,204 (class II), or US \$297 (class I) annually,” the authors note.

The authors addressed guidelines to consider bariatric surgery in all obese patients. They recommend

SG remain the standard of care for patients with severe obesity.

But national projections show that SG would address only 0.5% of life-years lost due to obesity.

“Barring a dramatic increase in patient adherence, bariatric surgery will not likely successfully mitigate the harm from the obesity epidemic. ESG may fill this gap and provide an additional option for patients with obesity as it demonstrated sustained weight loss at 2-5 years.”

While insurance coverage is

limited, they write, “our model demonstrates that payer coverage for ESG would provide an alternative tool to combat the obesity epidemic as part of a multidisciplinary approach.”

Semaglutide shows sustained weight loss in trials for up to 2 years but has a substantial annual cost, the authors note.

One limitation to the study is a lack of long-term data available for ESG and semaglutide. Authors were also not able to use a lifetime

horizon because of a lack of long-term weight loss.

One study author reports financial relationships with BSC, Cook Medical, Surgical Intuitive, and Olympus America. Another author reports relationships with ACI, AGA-Varia, BSC, Dark Canyon Labs, Endiatx, Medtronic, Olympus, and Virgo Systems, as well as equity in AGA-Varia, Dark Canyon Labs, Endiatx, EndoSound, and Virgo Systems. The rest of the authors have no conflicts to disclose. ■



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