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GI&Hepatology News

December 2024

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MASH: Experts Offer Noninvasive Cutoffs for Prescribing Resmetirom

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

An expert panel has published noninvasive test (NIT) cutoffs to identify patients with metabolic dysfunction–associated steatohepatitis (MASH) with stage 2 or 3 fibrosis who may benefit from resmetirom therapy.

This guidance document allows clinicians to use a variety of NITs to start and monitor resmetirom therapy, precluding the need for a biopsy, lead author Mazen Noureddin, MD, of Houston Research Institute, Houston Methodist Hospital in Texas, and colleagues reported.

"The recent conditional approval by the [Food and Drug Administration] of resmetirom ... presents a much-anticipated therapeutic option for patients with noncirrhotic advanced MASH," the investigators wrote in *Clinical Gastroenterology and Hepatology* (2024 Jul. doi: 10.1016/j.cgh.2024.07.003).

However, the approval also "presents important challenges," they noted, "including how to noninvasively identify patients with fibrosis stages 2-3 [F2-F3], and how to exclude patients with more advanced disease who should not be treated until further data emerge on the use of resmetirom in this population."

To help identify which patients should get this new intervention, Noureddin and colleagues considered

See **Resmetirom** · *page 26*

GI Docs Will Need to Forge a 'Human-Computer Cooperative'

LEISA THOMPSON

Dr. Ryan W. Stidham

BY JOHN WATSON

Several artificial intelligence (AI) technologies are emerging that will change the management of gastrointestinal (GI) diseases sooner rather than later. One of the leading researchers working toward that AI-driven future is Ryan W. Stidham, MD, MS, AGAF, associate professor of gastroenterology and computational medicine and bioinformatics at the University of Michigan, Ann Arbor.

Dr. Stidham's work focuses on leveraging AI to develop automated systems that better quantify disease activity and aid gastroenterologists in their decision-making. He also serves as a member of AGA's AI Task Force. He spoke with *GI & Hepatology News* about how his efforts could shape AI into a tool with practical applications in gastroenterology, what the technology may do to improve physician efficiency, and why gastroenterologists shouldn't be worried about being replaced by machines any time soon.

How did you first become involved in studying AI applications for GI conditions?

My medical training coincided with the emergence of electronic health records (EHRs) making enormous amounts of data, ranging from laboratory results to diagnostic codes and billing records, readily accessible.

I quickly contracted data analytics fever, but a major problem became apparent: EHRs

See **Cooperative** · *page 20*

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LETTER FROM THE EDITOR

Physicians as Advocates

As physicians, we hold positions of power and privilege in society. With that power and privilege comes a sacred responsibility to serve as healthcare advocates, for our individual patients as well as for our larger communities in helping them navigate the complexities of the healthcare system and recognize and address barriers to care.

In addition to delivering high-quality, patient-centered care in our clinics and endoscopy units, it is imperative that gastroenterologists use our individual and collective voice in promoting policy reforms that improve healthcare access, affordability, and equity, and help the healthcare system work better for our patients.

Dr. Adams

'As a new slate of elected officials prepares to take office in January, I hope you will join me in considering how best to use your voice as a physician to promote systemic change.'

Particularly in the wake of Election Day, it is critical to realize the power of physician advocacy in informing rational policymaking relating to healthcare. In furtherance of this goal, AGA held its largest ever Advocacy Day this Fall, bringing together more than 100 members and patient advocates from 28 states to educate members of Congress and their staff about policies affecting GI patient care, including prior authorization, step therapy, federal research funding, and Medicare reimbursement. As a new slate of elected officials prepares to take office in January, I hope you will join me in considering how best to use your voice as a physician to promote systemic change, whether through participating in a future AGA Congressional Advocacy Day, or by meeting independently with your local, state, or federal elected officials to discuss the issues critical to the well-being of your patients and communities. Now more than ever, physician advocacy is critical to achieving a high-performing healthcare system.

In GIHN's December issue, we highlight expert guidance on the use of noninvasive markers in prescribing resmetirom for MASH and summarize a recent systematic review revealing a link between environmental pollutant exposure and inflammatory bowel disease. In our Member Spotlight column, Dr. Jeffrey Lee (Kaiser Permanente N. California) updates us on his innovative research on colorectal cancer prevention. We hope you have a wonderful holiday season with your friends and family and look forward to seeing you again in 2025!

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

Call for Nominations

Member SPOTLIGHT

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

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Live Rotavirus Vaccine Safe for Newborns of Biologic-Treated Moms With IBD

BY DIANA SWIFT

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

More evidence suggests there is little risk in administering the live rotavirus vaccine to the babies of mothers on biologics during pregnancy for inflammatory bowel disease (IBD).

No adverse events or impairment of the immune system emerged in babies at 7 days, 1 month, and 9 months post vaccination, in findings from a small Canadian study published in *Clinical Gastroenterology and Hepatology* (2024 July. doi: 10.1016/j.cgh.2024.07.007).

The study found normal extended immune function testing in infants despite third-trimester maternal biologic therapy and regardless of circulating drug levels. The data provide reassurance about live rotavirus vaccination in this population and may also offer insights into the safety of other live vaccines in biologic-exposed individuals, wrote investigators led by gastroenterologist Cynthia H. Seow, MD, a professor in the Cumming School of Medicine at the University of Calgary in Alberta, Canada.

Dr. Seow

'Despite the well-established safety and effectiveness of non–live vaccination in individuals with IBD ... vaccine uptake in pregnant women with IBD and their infants remains suboptimal.'

"Despite the well-established safety and effectiveness of non–live vaccination in individuals with IBD and their infants remains suboptimal," Seow said in an interview. This largely arises from maternal and physician concerns regarding transplacental transfer of IBD therapies and their impact on the safety of vaccination.

"These concerns were heightened after reports emerged of five fatal outcomes following the administration of the live Bacille Calmette-Guérin [BCG] vaccine in biologic-exposed infants. However, it had already been reported that inadvertent administration of the live oral rotavirus vaccine, a very different vaccine in terms of target and mechanism of action, in biologic-exposed individuals had not been associated with significant adverse effects," she said.

They undertook their analysis with the hypothesis that vaccination would carry low risk, although the live oral vaccine is not currently recommended in biologic-exposed infants. "Yet rotavirus is a leading cause of severe, dehydrating diarrhea in children under the age of 5 years globally, and vaccination has led to significant reductions in hospitalizations and mortality," Seow added.

Provision of the vaccine to anti–tumor necrosis factor (TNF)–exposed infants has been incorporated into the Canadian Public Health and Immunization guidelines, as the majority of the biologic-exposed infants were exposed to anti-TNF agents. "And with collection of further data, we expect that this will be extended to other biologic agent exposure. These data are important to pregnant women with IBD as they help to normalize their care. Pregnancy is difficult enough without having to remember exceptions to care," Seow said.

"Before some of the studies came out, broad guidelines recommended that live vaccines should not be used in biologic-exposed infants, but this had been thought to be overly zealous and too conservative, and the risk was thought to be low," said Elizabeth Spencer, MD, an assistant professor of pediatrics in the Division of Pediatric Gastroenterology at the Icahn School of Medicine at Mount Sinai in New York City, in an interview. Spencer was not involved in the Canadian study.

Dr. Spencer

'At our center, we had some moms on biologics during pregnancy who forgot and had their babies vaccinated for rotavirus, and the babies were all fine.'

"At our center, we had some moms on biologics during pregnancy who forgot and had their babies vaccinated for rotavirus, and the babies were all fine," she said.

The safety of this vaccine has been confirmed by several small studies and recently the PIANO Helmsley Global Consensus on Pregnancy and Inflammatory Bowel Disease, which was presented at Digestive Disease Week 2024. The consensus encompasses preconception counseling and the safety of IBD medications during pregnancy and lactation.

"Another concern, however, was that giving a live [gastrointestinal] bug like rotavirus to babies might overstimulate their immune systems and provoke IBD," Spencer added. "While a number of population-based studies in the US and Europe showed that was not the case, at least in the general population, there was a suggestion that, down the road, vaccination might be mildly protective against IBD in some cases."

She added the caveat that these studies were not done in mothers and their babies with IBD, who might be inherently at greater risk for IBD. "So, a question for future research would be, 'Is immune stimulation of the gut in IBD moms and their babies a good or a bad thing for their gut?' "

Spencer conceded that "the data present a bit of a blurry picture, but I think it's always better just to vaccinate according to the regular schedule. The current data say there is no added risk, but it would be nice to look specifically at risk in moms with IBD and their children."

The Study

The prospective cohort study is a substudy of a larger 2023 one that included biologic use in a range of maternal illnesses, not just IBD (Lancet Child Adolesc Health. 2023 Sep;7[9]:648-656).

For the current study, Seow and colleagues identified 57 infants born to 52 mothers with IBD attending a pregnancy clinic at the University of Calgary in the period 2019-2023. Almost 81% of the mothers had Crohn's disease, and the median duration of IBD was 10 years. The median gestational age at delivery was 39 weeks, and almost 60% of deliveries were vaginal. The infants had been exposed in utero to infliximab (n = 21), adalimumab (n = 19), vedolizumab (n = 10), and ustekinumab (n = 7) in the third trimester.

The 57 biologic-exposed infants underwent standardized clinical assessments, drug concentration, and immune function testing. The live oral rotavirus vaccine series was provided to 50 infants, with the first dose at a median of 13 weeks of age. Immunologic assessments validated for age were normal in all infants despite median infliximab concentrations of 6.1 µg/mL (range, 0.4-28.8 µg/mL), adalimumab concentrations of 1.7 µg/mL (range, 0.7-7.9 µg/mL), ustekinumab concentrations of 0.6 µg/mL (range, 0-1.1 µg/mL), and undetectable for vedolizumab at 10.7 weeks of age.

As anticipated, infant immune function was normal regardless of circulating drug levels.

The overall message, said Seow, is "healthy mum equals healthy baby. Be more concerned regarding active inflammation than active medications. In almost all circumstances, treat to target in pregnancy as you would in the nonpregnant state." She added, however, that further studies are needed to determine the safety and optimal timing of other live vaccines, such as the BCG, in the presence of biologic therapy.

This study was funded by the Alberta Children's Hospital Research Institute. Seow reported advisory/speaker's fees for Janssen, AbbVie, Takeda, Pfizer, Fresenius Kabi, Bristol-Myers Squibb, Pharmascience, and Lilly, as well as funding from Alberta Children's Hospital Research Institute, Crohn's and Colitis Canada, the Canadian Institutes of Health Research, and Calgary Health Trust, and data safety monitoring from New South Wales Government Health, Australia. Multiple coauthors disclosed similar consulting or speaker relationships with private industry. Spencer had no competing interests with regard to her comments. ■

Environmental Pollutants Play a Growing Role in IBD

BY DIANA SWIFT

In a review of 32 mixed-type human studies, multinational researchers found a growing association between various classes of environmental pollutants and the risk for inflammatory bowel disease (IBD).

The culprit environmental substances include heavy and transition metals, air pollutants, pesticides, and industrial contaminants. The latter encompass synthetic chemicals such as perfluoroalkyls and polyfluoroalkyls (PFAs), which are present in many common household products.

In contrast, zinc exposure may have a protective, anti-inflammatory effect, according to a research group led by Maria Manuela Estevinho, MD, of the Department of Gastroenterology of the Unidade Local de Saúde Gaia e Espinho in Vila Nova de Gaia, Portugal.

Dr. Agrawal

'At the individual level, we can try to decrease our exposure to chemicals; for example, to minimize use of pesticides and products containing synthetic chemicals in our homes.'

Published in *Gut* (2024 Aug. doi: 10.1136/gutjnl-2024-332523), the review also found limited data suggesting adverse IBD outcomes such as hospitalizations are more prevalent with increased exposure to air contaminants in particular.

"These data carry relevance toward counseling patients and family members," coauthor Manasi Agrawal, MD, assistant professor of medicine at the Icahn School of Medicine, Mount Sinai, and a gastroenterologist at Mount Sinai Hospital in New York City, said in an interview. "At the individual level, we can try to decrease our exposure to chemicals; for example, to minimize use of pesticides and products containing synthetic chemicals in our homes. However, at the broader community level, health policy changes are needed to help with mitigation strategies and to curb production."

The physiological mechanisms by which pollutants raise IBD risk include an exaggerated immune response leading to systemic inflammation, loss of tight junction proteins leading to increased gut permeability, and dysbiosis of the intestinal microbiota.

The review found the following effects for various pollutants:

- Heavy and transition metals such as copper, lead, and cadmium were associated with gut dysbiosis, overgrowth of undesirable species of microorganisms, and loss of tight junction proteins leading to leaky gut. In all studies, individuals with IBD showed higher concentrations of such metals than healthy control individuals. While the specific profile of heavy metals varied across studies, lead, copper, and iron, were linked to IBD risk in more than one study.
- The particulate matter present in air pollution — including agricultural and wood dust as well as volcanic ash and hydrocarbon dioxin — was linked to dysbiosis and tight junction protein loss. Air pollution has also been linked to increased incidence of irritable bowel syndrome.
- Industrial and organic pollutants such as perfluoroalkyl and polyfluoroalkyl compounds, triclocarban, and polychlorinated biphenyls were also associated with gut permeability and/or reduced microbial diversity.
- Pesticides such as PFAs, organochloride and organophosphate compounds, and pyrethroids were associated with loss of tight junction proteins.
- Zinc was linked to an increase in tight junction proteins.

Commenting on the review but not involved in it, Ashwin N. Ananthakrishnan, MBBS, MD, MPH, AGAF, director of the Crohn's and Colitis Center at Massachusetts General Hospital, and associate professor at Harvard Medical School in Boston, called it a very important study that expands our understanding of the role of environment in IBD.

"While traditionally studies have focused on dietary and other exposures related to personal behavior and lifestyle such as smoking, this expands consideration to exposures at the environmental level, where an individual may have less control," he said in an interview.

THOMAS321/GETTY IMAGES

Air pollution from coal- and oil-fired power plants contains more than 80 hazardous air pollutants required for control under the Clean Air Act, including arsenic, chromium, lead, formaldehyde, acid gases, dioxins, and furans.

"This shift could be critically important from a policy standpoint as modifying these risk factors may require more societal than individual efforts," he added. He did offer a caveat, however. "While the review highlights several plausible associations, all of which merit further study, importantly, one should also avoid overinterpreting the results as there are very few high-quality studies that provide robust evidence of an association. So more work is needed."

Recent research has suggested that environmental exposures affect IBD risk more than genetic predisposition.

Dr. Ananthakrishnan

'While the review highlights several plausible associations, all of which merit further study ... one should also avoid overinterpreting the results as there are very few high-quality studies that provide robust evidence of an association.'

As background to this review, the growing industrialization and consumerism of the developing world has seen the global number of IBD cases rise from 3.3 million in 1990 to an estimated 4.9 million in 2019, a jump of 47.5%. In the United States, IBD accounts for more than $25 billion in direct healthcare costs.

In terms of the near future, Dr. Agrawal said, "Next steps would be to measure various chemicals in pre-disease biological samples for objective assessment of the impact of chemicals on IBD risk, and such studies are already underway."

That would mean using exposure biomarkers with high temporal resolution in preclinical samples, as well as advanced measurement techniques and machine-based composite data analysis to explain the IBD-pollutant relationship. "This approach may also provide insight into the role of different environmental insults in different stages of life and clarify whether the timing of exposure may be more critical than the duration," the authors wrote.

Dr. Agrawal was supported by the National Institute of Diabetes and Digestive and Kidney Diseases, the International Organization for the Study of Inflammatory Bowel Disease, and the Crohn's and Colitis Foundation. She reported consulting for Douglas Pharmaceuticals. Other authors reported lecture/consulting fees from multiple pharmaceutical/biomedical companies. Dr. Ananthakrishnan had no relevant conflicts of interest. ■

EPI: Optimal PERT Dose Varies by Primary Disease

BY BECKY MCCALL

FROM UEG 2024

VIENNA, AUSTRIA — The appropriate dose of pancreatic enzyme replacement therapy (PERT) for exocrine pancreatic insufficiency (EPI) depends on the root cause of the insufficiency, according to results of a prospective study using European registry data.

Specifically, patients with EPI caused by pancreatic cancer or pancreatectomy need significantly more enzyme replacement than patients with insufficiency caused by chronic pancreatitis and acute pancreatitis. The need to add a proton pump inhibitor (PPI) to achieve the therapeutic goal also varies by condition, the study showed.

One of the main symptoms of EPI is malnutrition, and successful PERT is defined as the resolution of nutritional deficiencies and relief of symptoms and signs associated with insufficiency, said Enrique Domínguez Muñoz, MD, director of gastroenterology and hepatology at University Hospital of Santiago de Compostela, Spain.

Our findings show that, "in order to achieve this, enzyme dose escalation and sometimes additional treatment with a [PPI] should be applied as required by the individual", he reported in a presentation at the United European Gastroenterology (UEG) Week 2024.

Therefore, having dose recommendations for PERT for different causes of EPI is very helpful, said Domínguez Muñoz.

Pancreatic enzyme preparations, specifically pancreatin, are the recommended first-line treatment for EPI, but the initial doses of PERT vary depending on the patient's age, severity of the insufficiency, and fat content of the meal eaten.

Dr. Domínguez Muñoz

Domínguez Muñoz and colleagues wanted to explore whether — and how — the severity of EPI varied with different diseases, therefore varying the optimal dose of PERT.

Optimal Dosing

The prospective study drew on data from a European registry of patients diagnosed with EPI treated with PERT in expert centers.

The researchers evaluated the dose of PERT required to achieve symptom relief and normalization of the nutritional status in adult patients with EPI secondary to different pancreatic diseases and conditions. The percentage of patients who required the addition of a PPI to PERT to achieve the therapeutic goal was also determined.

Decisions on the initial enzyme dose (including the addition of a PPI) and any necessary adjustments during follow-up to achieve the therapeutic goal were made by the participants' clinicians.

A total of 678 patients (mean age, 61.2 ± 13.8 years; 63.6% male) were stratified according to disease: 50% had chronic pancreatitis, 10% had acute pancreatitis, 17% had undergone pancreaticoduodenectomy, 15% had pancreatic cancer, and 8% had another pancreatic condition.

To achieve the therapeutic goal, the median optimal enzyme doses with the main meal for patients

Continued on following page

Value of AI-Aided Colonoscopy on Advanced Neoplasia Detection Unclear

BY MEGAN BROOKS

A new meta-analysis confirms that use of computer-aided detection (CADe) systems during colonoscopy finds more polyps and adenomas than conventional colonoscopy, but the effect on detection of advanced colorectal neoplasia (ACN) remains unclear.

The research team, which focused on advanced neoplasia because of their clinical importance, found a small increase in the ACN detection rate with CADe but no difference in ACNs detected per colonoscopy.

Dr. Shung

'The large sample size included in this study allowed us to examine efficacy of CADe in diagnosis of clinically relevant colonic lesions more accurately.'

Dr. Glissen Brown

'The study of CADe has made the field of gastroenterology a clinical leader when it comes to the number of high-quality randomized trials examining AI interventions.'

For ACN, "the ones we really care about, the findings were discordant," Dennis Shung, MD, PhD, MHS, with Yale School of Medicine, New Haven, Connecticut, said in an interview.

There was a "small positive signal" indicating the potential of artificial intelligence (AI) to detect advanced neoplasia. "However, we can't say for sure that it will help you find advanced colonic neoplasia," Shung said.

Jeremy Glissen Brown, MD, MSc, gastroenterologist with Duke Health, Durham, North Carolina, who wasn't involved in the study, said in an interview that it's "one of the most comprehensive systematic reviews and meta-analyses to date, examining both parallel and tandem randomized clinical trials [RCTs] of CADe in colonoscopy."

"The results are generally consistent with prior RCTs and meta-analyses and show an improvement in important quality metrics, mainly an increase in adenomas per colonoscopy [APC], an increase in adenoma detection rate [ADR], and a decrease in adenoma miss rate [AMR]," he noted.

The analysis was published online in *Annals of Internal Medicine* (2024 Oct. doi: 10.7326/ANNALS-24-00981).

Larger, More Accurate Analysis

Prior meta-analyses of AI-assisted colonoscopy included up to 33 RCTs. In their updated meta-analysis, Shung and colleagues included 44 RCTs with 36,201 cases.

"The large sample size included in this study allowed us to examine efficacy of CADe in diagnosis of clinically relevant colonic lesions more accurately, which was not feasible in prior RCTs and reviews given lower sample size," they wrote.

For polyp detection, CADe-enhanced colonoscopy outperformed conventional colonoscopy in the average number of polyps detected per colonoscopy (1.59 vs 1.27; incidence rate difference [IRD], 0.35) and polyp detection rate (54% vs 46.5%; rate ratio [RR], 1.21).

The same held true for adenoma detection. CADe-enhanced colonoscopy had a higher average APC (0.98 vs 0.78; IRD, 0.22) and ADR (44.7% vs 36.7%; RR, 1.21), coupled with a lower AMR (16.1% vs 35.3%; RR, 0.47).

Average ACN per colonoscopy was similar with and without CADe enhancement (0.16 vs 0.15; IRD, 0.01), but there was a small increase in the ACN detection rate (12.7% vs 11.5%; RR, 1.16).

Results of a subgroup analysis suggest decreased benefit of CADe in patients with positive fecal immunochemical test results, "which may indicate an attenuated benefit for the use of CADe systems for regular screening practice," the study team wrote.

In a sensitivity analysis of overall adenoma detection according to baseline ADR, there was an increase in the benefit of CADe systems among providers with a lower ADR.

Use of CADe systems led to resection of nearly two extra nonneoplastic polyps per 10 colonoscopies and a "marginal" increase in withdrawal time (0.53 minutes) that may have "limited clinical significance," the authors noted.

There were no clear differences in performance between the different CADe systems used in the included studies.

All studies were rated as "high concern" for overall bias. Other limitations include study heterogeneity, absence of blinding between conventional and CADe-enhanced colonoscopies, and unaccountable confounding factors.

Ready for Prime Time?

Is routine adoption of AI-assisted colonoscopy ready for prime time? Glissen Brown thinks so, with some caveats.

"We are at a pivotal point in the examination CADe for routine use in colonoscopy. CADe has been ready for prime time in the United States since at least 2021, and the study of CADe has made the field of gastroenterology a clinical leader when it comes to the number of high-quality randomized trials examining AI interventions," Glissen Brown said.

However, outside of the clinical trial setting, questions about successful deployment and implementation remain, he said.

"These include but are in no way limited to ways to optimize the AI-human interaction in order to produce a successful AI-provider partnership, issues of reimbursement and cost, and issues of ethical AI development and deployment," Glissen Brown said.

"We also need to continue to assess methods of estimating CADe use on the downstream outcomes that matter, such as the effects of CADe on reducing rates of colon cancer, rates of post-colonoscopy colorectal cancer (CRC), and the effect that CADe might have on CRC-related mortality. In addition, more studies on the patient voice and patient preference as it relates to AI use are greatly needed," Glissen Brown said.

The American Gastroenterological Association has drafted recommendations on the use of CADe systems during colonoscopy. Clinicians are invited to review the draft guideline on the AGA website.

The study had no specific funding. Disclosures for study authors are available with the original article. Glissen Brown is a consultant for Medtronic, Olympus, and Odin Vision. He was also the lead author on one of the studies included in the meta-analysis.

Continued from previous page

with acute pancreatitis, chronic pancreatitis, pancreatic cancer, and pancreaticoduodenectomy were 40,000, 50,000, 70,000, and 75,000 PhU, respectively. The respective optimal daily enzyme doses were 100,000, 150,000, 210,000, and 225,000 PhU.

The highest enzyme doses required with the main meal to achieve the therapeutic goal for patients with acute pancreatitis, chronic pancreatitis, pancreatic cancer, and pancreaticoduodenectomy were 125,000, 210,000, 175,000, and 210,000 PhU, respectively. The respective highest daily enzyme doses were 400,000, 625,000, 675,000, and 750,000 PhU.

The need for additional therapy with twice-daily PPI to achieve the therapeutic goal also varied according to the underlying disease. It was administered to 44.1% of patients with acute pancreatitis, 37.2% of patients with chronic pancreatitis, 78.8% of patients with pancreatic cancer, and 74.1% of patients who had undergone pancreaticoduodenectomy.

"This shows us that sometimes we really do need to significantly increase the dose of pancreatic enzyme replacement therapy," Domínguez Muñoz said.

Domínguez Muñoz reports receiving speaking and consultancy fees from Viatris, Abbott Pharmaceuticals, and Boston Scientific.

Kris V. Kowdley, MD, AGAF, FAASLD, FACP, FACG

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US-DS-2400079 December 2024

Primary Sclerosing Cholangitis (PSC) and Its Importance in Clinical Practice

Primary sclerosing cholangitis (PSC) is a rare, chronic, and progressive cholestatic liver disorder.[1] Commonly associated with pruritus, an intense itch that significantly impacts patients' lives, PSC is characterized by inflammation, fibrosis, and stricturing of the intrahepatic and/or extrahepatic bile ducts.[1,2] The natural history of PSC is highly variable, but disease progression frequently leads to end-stage liver disease, with liver transplantation as the only currently available treatment option.[1,2] PSC has a close association with inflammatory bowel disease (IBD), with approximately 60% to 80% of patients with PSC having a diagnosis of either ulcerative colitis or Crohn's disease.[1,3] Although the exact pathogenesis of PSC is still under investigation, evidence suggests a complex interplay of genetic susceptibility, immune dysregulation, and environmental factors may be responsible.[4]

PSC is considered a rare disease, with an estimated global median incidence of 0.7 to 0.8 per 100,000 and estimated prevalence of 10 cases per 100,000.[5] PSC is more common in men (60% to 70%), with men having a 2-fold higher risk of developing PSC than women.[2,6,7] The majority of patients are diagnosed between the ages of 30 to 40 years, with a median survival time after diagnosis without a liver transplant of 10 to 20 years.[2,7-9]

Signs and Symptoms of PSC

Approximately 50% of patients with PSC are asymptomatic when persistently abnormal liver function tests trigger further evaluation.[1,2,10] Patients may complain of pruritus, which may be episodic; right upper quadrant pain; fatigue; and jaundice.[2,7] Fevers, chills, and night sweats may also be present at the time of diagnosis.[2]

Pruritus and fatigue are common symptoms of PSC and can have a significant impact on the lives of patients.[5] The pathogenesis of pruritus is complex and not completely understood but is believed to be caused by a toxic buildup of bile acids due to a decrease in bile flow related to inflammation, fibrosis, and stricturing resulting from PSC.[11,12]

Pruritus has been shown to have a substantial impact on patients' health-related quality of life (QoL), with greater impairment seen with increased severity of pruritus.[13] Specifically, patients with pruritus report physical limitations on QoL-specific questionnaires, as well as an impact on emotional, bodily pain, vitality, energy, and physical mobility measures.[14]

From a multinational survey on the impact of pruritus in PSC patients, 96% of respondents indicated that their itch was worst in the evening, with 58% indicating mood changes, including anxiety, irritability, and feelings of hopelessness due to their itch. Further, respondents reported that their pruritus disrupted their day-to-day responsibilities and that this disruption lasted 1 month or more.[15]

The psychological impact of living with PSC has not been well studied, although it has been found that individuals living with the disease demonstrated a greater number of depressive symptoms and poorer well-being, often coinciding with their stage of liver disease and comorbidity with IBD.[16]

In those living with PSC, mental health-related QoL has been shown to be influenced by liver disease, pruritus, social isolation, and depression. In one study, nearly 75% of patients expressed existential anxiety regarding disease progression and shortened life expectancy, with 25% disclosing social isolation.[13]

Diagnosing PSC

PSC should be considered in patients with a cholestatic pattern of liver test abnormalities, especially in those with underlying IBD. Abnormalities that may be detected on physical examination include jaundice, hepatomegaly, splenomegaly, and excoriations from scratching.[3,5] PSC and autoimmune hepatitis (AIH) may coexist, particularly in younger patients, with serum biochemical tests and autoantibodies suggestive of AIH.[2] Most patients demonstrate elevated serum alkaline phosphatase levels, as well as modest elevation of transaminases.[2] Bilirubin and albumin levels may be normal at the time of diagnosis, although they may become increasingly abnormal as the disease progresses.[2] A subset of patients (10%) may have elevated levels of immunoglobulin G4 (IgG4) and tend to progress more rapidly in the absence of treatment.[2] Autoantibodies, which are characteristic of primary biliary cholangitis (PBC)—another rare, chronic, and progressive liver disease—are usually absent in PSC. When present, autoantibodies are of unknown clinical significance.[2,17]

Imaging, including cross-sectional imaging, particularly magnetic resonance cholangiopancreatography, is often used to the biliary tree in patients with persistently abnormal cholestatic tests.[2] A diagnosis of PSC is typically established by the demonstration of characteristic multifocal stricturing and dilation of intrahepatic and/or extrahepatic bile ducts on cholangiography.[5] The diagnosis of PSC is occasionally made on liver biopsy, which may reveal characteristic features of "onion skin fibrosis" and fibro-obliterative cholangitis when cholangiography is normal. In this circumstance, it is classified as "small-duct PSC."[5,18]

Table 1: Histologic and Radiologic Features of PSC

Clinical Features	Prevalence
Strictures in intrahepatic and extrahepatic bile ducts	87%
Strictures in intrahepatic bile ducts alone	11%
Strictures in extrahepatic bile ducts alone	2%
Gallbladder and cystic duct abnormalities	41%

Biliary strictures in patients with PSC may be focal, with normal intervening areas, or diffuse, involving long segments. Strictures can occur in any part of the biliary tree.[5,20,21]

Treatment and Management of PSC

Despite advances in our understanding of PSC, there are currently no approved drug therapies for PSC and no approved treatments for PSC-associated pruritus. The American Association for the Study of Liver Diseases (AASLD) published the most recent practice guidance for the treatment and management of PSC in 2022.[7]

Ursodeoxycholic acid (UDCA) has been widely studied as a potential PSC treatment. While UDCA demonstrates improvements in biochemical measures, there has been a lack of evidence demonstrating clinical improvement.[19]

The role of UDCA in the

treatment of PSC is unclear and, at this time, is not supported by the American College of Gastroenterology or AASLD.[2,7] Additional treatments, including immunosuppressive medications (methotrexate, tacrolimus), corticosteroids (prednisolone), and antibiotics (minocycline, vancomycin) have been explored but have not shown definitive clinical benefit.[2]

UDCA, if used, should not be prescribed at doses in excess of 20 mg/kg/day since high-dose UDCA (28-30 mg/kg) was associated with adverse liver outcomes.[2]

Although there are no therapies approved specifically to manage PSC-associated pruritus, cholestyramine and rifampin have been shown to be beneficial in relieving itch in some patients.[22] In a survey of PSC patients, one in three reported suffering from pruritus during the previous week. It is possible that the prevalence and severity of pruritus in PSC may be under-recognized compared with PBC, given that patients and physicians may be focused on the many other medical issues that are often prioritized over symptoms, such as concern about cancer risk and need for frequent surveillance procedures.[15,23] Discussions between patients and physicians are important to deepen our understanding of the prevalence of pruritus and its burden on the lives of patients.

Novel therapies for PSC and PSC-associated pruritus, including a selective inhibitor of the ileal bile acid transporter (IBAT), are currently being explored in clinical trials. Research suggests that the inhibition of IBAT blocks the recycling of bile acids, which reduces bile acids systemically and in the liver. Early clinical studies demonstrated on-target fecal bile acid excretion, a pharmacodynamic marker of IBAT inhibition, in addition to decreases in low-density lipoprotein cholesterol and increases in 7αC4, which are markers of bile acid synthesis.[24]

To learn more about ongoing clinical trials, please visit https://www.mirumclinicaltrials.com.

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Member SPOTLIGHT

Searching for the Optimal CRC Surveillance Test

BY JENNIFER LUBELL
MDedge News

About a third of the US population is eligible for colorectal cancer (CRC) screening but aren't up to date on the tests.

Many patients are reluctant to test for colon cancer for a variety of reasons, said Jeffrey K. Lee, MD, MPH, a research scientist at the Kaiser Permanente Northern California Division of Research and an attending in gastroenterology (GI) at Kaiser Permanente San Francisco (SF) Medical Center.

"As a gastroenterologist, I strongly believe we should emphasize the importance of colorectal cancer screening. And there's many tests available, not just a colonoscopy, to help reduce your chances of developing colorectal cancer and even dying from colorectal cancer," said Lee.

Many patients prefer a test that's more convenient, that doesn't require them to take time out of their busy schedules. "We must educate our patients that there are some noninvasive screening options that are helpful, and to be able to share with them some of the benefits, but also some of the drawbacks compared to colonoscopy and allow them to have a choice," he advised.

Courtesy Dr. Jeffrey K. Lee

Dr. Jeffrey K. Lee, a graduate of the University of California (UC), Berkeley, is pictured here with his son at a 2024 Cal football game.

Lee has devoted his research to colorectal cancer screening, as well as the causes and prevention of CRC. He is a recipient of the AGA Research Scholar Award, and has in turn supported other researchers by contributing to the AGA Research Foundation. In 2012, Lee received a grant from the Sylvia Allison Kaplan Clinical Research Fund to finance a study on long-term colorectal cancer risk in patients with normal colonoscopy results.

The findings, published in *JAMA Internal Medicine* (2018 Dec. doi: 10.1001/jamainternmed.2018.5565), determined that 10 years after a negative colonoscopy, Kaiser Permanente members had a 46% lower risk of being diagnosed with CRC and were 88% less likely to die from disease compared with patients who didn't undergo screening.

"Furthermore, the reduced risk of developing colorectal cancer, even dying from it, persisted for more than 12 years after the examination compared with an unscreened population," said Lee. "I firmly believe our study really supports the 10-year screening interval after a normal colonoscopy, as currently recommended by our guidelines."

In an interview, he discussed his research efforts to find the best detection regimens for CRC, and the mentors who guided his career path as a GI scientist.

Q: Why did you choose GI?
During medical school I was fortunate to work in the lab of John M. Carethers, MD, at UC San Diego. He introduced me to GI and inspired me to choose GI as a career. His mentorship was invaluable because he not only solidified my interest in GI, but also inspired me to become a physician scientist, focusing on colorectal cancer prevention and control. His amazing mentorship drew me to this field.

Q: One of your clinical focus areas is hereditary gastrointestinal cancer syndromes. How did you become interested in this area of GI medicine?
My interest in hereditary GI cancer syndromes stemmed from my work as a medical student in Carethers' lab. One of my research projects was looking at certain gene mutations among patients with hereditary GI cancer syndromes, specifically, familial hamartomatous polyposis syndrome. It was through these research projects and seeing how these genetic mutations impacted their risk of developing colorectal cancer that inspired me to care for patients with hereditary GI cancer syndromes.

Q: Have you been doing any research on the reasons why more young people are getting colon cancer?
We recently published work (Clin Gastroenterol Hepatol. 2024 Oct. doi: 10.1016/j.cgh.2024.09.002) looking at the potential factors that may be driving the rising rates of early-onset colorectal cancer. One hypothesis that's been floating around is antibiotic exposure in early adulthood or childhood because of its effect on the microbiome. Using our large database at Kaiser Permanente Northern California, we did not find an association between oral antibiotic use during early adulthood and the risk of early-onset colorectal cancer.

'During medical school I was fortunate to work in the lab of John M. Carethers, MD, at UC San Diego. He introduced me to GI and inspired me to choose GI as a career. His mentorship was invaluable.'

You have the usual suspects like obesity and diabetes, but it's not explaining all that risk. While familial colorectal cancer syndromes contribute to a small proportion of early-onset colorectal, these syndromes are not increasing across generations. I really do feel it's

Continued on following page

LIGHTNING ROUND

Texting or talking?
Text

Favorite breakfast?
Taiwanese breakfast

Place you most want to travel to?
Japan

Favorite junk food?
Trader Joe's chili lime chips

Favorite season?
Springtime, baseball season

Favorite ice cream flavor?
Mint chocolate chip

Number of cups of coffee you drink per day?
2-3

Last movie you watched?
Oppenheimer

Best place you ever went on vacation?
Hawaii

If you weren't a gastroenterologist, alternative career?
Barber

Best Halloween costume you ever wore?
SpongeBob SquarePants

Favorite sport?
Tennis

Song you have to sing along with when you hear it?
Any classic 80s song

Introvert or extrovert?
Introvert

AGA Research Foundation: You Can Help

BY MICHAEL CAMILLERI, MD, DSC, AGAF

To my fellow AGA Members, I'm not the first to tell you that real progress in the diagnosis, treatment, and cure of digestive disease is at risk. Research funding from traditional sources, like the National Institutes of Health, continues to shrink. We can expect even greater cuts on the horizon.

Gastroenterology (GI) investigators in the early stages of their careers are particularly hard hit. They are finding it much more difficult to secure needed federal funding. As a result, many of these investigators are walking away from GI research frustrated by a lack of support.

It is our hope that physicians have an abundance of new tools and treatments to care for their patients suffering from digestive disorders.

You know that research has revolutionized the care of many digestive disease patients. These patients, as well as everyone in the GI field clinicians and researchers alike, have benefited from the discoveries of passionate investigators, past and present.

This is where you can help.

New treatments and devices are the result of years of research. The AGA Research Foundation grants are critical to continuing the GI pipeline. The AGA research awards program helps researchers take new directions and discover new treatments to better patient care.

Help us fund more researchers by supporting the AGA Research Foundation with a year-end donation. Your donation will support young investigators' research careers and help ensure research is continued.

Be gracious, generous, and giving to the future of the GI specialty this holiday season. There are three easy ways to give:

Make a tax-deductible donation online at www.foundation.gastro.org.

Send a donation through the mail to:
AGA Research Foundation
4930 Del Ray Avenue
Bethesda, MD 20814

Or donate over the phone by calling (301) 222-4002. All gifts are tax-deductible to the fullest extent of US law. Join us! ■

Dr. Camilleri is AGA Research Foundation Chair and Past AGA Institute President. He is a consultant in the Division of Gastroenterology and Hepatology at the Mayo Clinic in Rochester, Minnesota.

Continued from previous page

something in the diet or how foods are processed and environmental factors that's driving some of the risk of early-onset colorectal cancer and this should be explored further.

Q: In 2018, you issued a landmark study (Gastroenterology. 2018 Nov. doi: 10.1053/j.gastro.2018.07.017) which found an association between a 10-year follow-up after negative colonoscopy and reduced risk of disease and mortality. Has there been any updates to these findings over the last 6 years?

We recently saw a study in *JAMA Oncology* (2024 May. doi: 10.1001/jamaoncol.2024.0827) of a Swedish cohort that showed a negative colonoscopy result was associated with a reduced risk of developing and even dying from colorectal cancer 15 years from that examination, compared to the general population of Sweden. I think there's some things that we need to be cautious about regarding that study. We have to think about the comparison group that they used and the lack of information regarding the indication of the colonoscopy and the quality of the examination. So, it remains uncertain whether future guidelines are going to stretch out that 10-year interval to 15 years.

Q: What other CRC studies are you working on now?

We have several studies that we are working on right now. One is called the PREVENT CRC study, which is looking at whether a polygenic risk score can improve risk stratification following adenoma removal for colorectal cancer prevention and tailoring post-polypectomy surveillance. This is a large observational cohort study that we have teamed up with the Fred Hutchinson Cancer Center, Erasmus University [Rotterdam, the Netherlands], and Kaiser Permanente Northwest to answer this important question that may have implications for personalized medicine.

Lee has devoted his research to the causes and prevention of CRC. He is a recipient of the AGA Research Scholar Award, and has in turn supported other researchers by contributing to the AGA Research Foundation.

Then there's the COOP study, funded by the Patient-Centered Outcomes Research Institute. This is looking at the best surveillance test to use among adults 65 years and older with a history of polyps. The trial is randomizing them to either getting a colonoscopy for surveillance or annual fecal immunochemical test for surveillance. This is to see which test is best for detecting colorectal cancer among older adults with a history of polyps.

Q: Do you think FIT tests could eventually replace colonoscopy, given that it's less invasive?

Although FIT and other stool-based tests are less invasive and have been shown to have high accuracy for detecting colorectal cancer, I personally do not think they are going to replace colonoscopy as the most popular screening modality in the United States. Colonoscopy remains the gold standard for detecting and removing precancerous polyps and has the highest accuracy for detecting colorectal cancer.

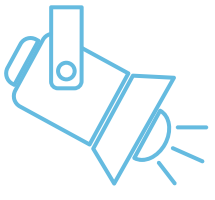
Q: Besides Carethers, what teacher or mentor had the greatest impact on you?

Clinically it's been Jonathan Terdiman, MD, from UCSF, who taught me everything I know about clinical GI, and the art of colonoscopy. In addition, Douglas A. Corley, MD, PhD, the Permanente Medical Group's chief research officer, has made the greatest impact on my research career. He's really taught me how to rigorously design a research study to answer important clinically relevant questions, and has given me the skill set to write NIH [National Institutes of Health] grants. I would not be here without these mentors who are truly giants in the field of GI.

Q: When you're not being a GI, how do you spend your free weekend afternoons? Are you still a "Cal Bears" fan at your alma mater, UC Berkeley?

I spend a lot of time taking my kids to their activities on the weekends. I just took my son to a Cal Bears Game Day, which was hosted by ESPN at Berkeley. It was an incredible experience hearing sports analyst Pat McAfee lead all the Cal chants, seeing Nick Saban from the University of Alabama take off his red tie and replace it with a Cal Bears tie, and watching a Cal student win a hundred thousand dollars by kicking a football through the goal posts wearing checkered vans. ■

Call for Nominations



Member SPOTLIGHT

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

AI-Assisted Future for GI

Cooperative *from page 1*

and medical claims data alone only weakly describe a patient. Researchers in the field were excited to use machine learning for personalizing treatment decisions for GI conditions, including inflammatory bowel disease (IBD). But no matter how large the dataset, the EHRs lacked the most rudimentary descriptions: What was the patient's IBD phenotype? Where exactly was the disease located?

'I wanted to use AI to retrieve that key information in text, images, and video that we use every day for IBD care, automatically interpreting the data like a seasoned gastroenterologist.'

I could see machine learning had the potential to learn and reproduce expert decision-making. Unfortunately, we were fueling this machine-learning rocket ship with crude data unlikely to take us very far. Gastroenterologists rely on data in progress notes, emails, interpretations of colonoscopies, and radiologists' and pathologists' reviews of imaging to make treatment decisions, but that information is not well organized in any dataset.

I wanted to use AI to retrieve that key information in text, images, and video that we use every day for IBD care, automatically interpreting the data like a seasoned gastroenterologist. Generating higher-quality data describing patients could take our AI models from interesting research to useful and reliable tools in clinical care.

How did your early research go about trying to solve that problem?

My GI career began amid the IBD field's shifting from relying on symptoms alone to objective biomarkers for IBD assessment, particularly focusing on standardized scoring of endoscopic mucosal inflammation. However, these scores were challenged with interobserver variability, prompting the need for centralized reading. More importantly, these scores are qualitative and do not capture all the visual findings an experienced physician appreciates when assessing severity, phenotype, and therapeutic effect. As a result, even experts could disagree on the degree of endoscopic severity, and patients with obvious differences in the appearance of mucosa could have the same endoscopic score.

I asked myself: Are we really using these measures to make treatment decisions and determine the effectiveness of investigational therapies? I thought we could do better and aimed to improve endoscopic IBD assessments using then-emerging digital image analysis techniques.

Convolutional neural network (CNN) modeling was just becoming feasible as computing performance increased. CNNs are well suited for complex medical image interpretation, using an associated "label," such as the presence or grade of disease, to decipher the complex set of image feature patterns characterizing an expert's determination of disease severity.

How did you convert the promise of CNN into tangible results?

The plan was simple: Collect endoscopic images from patients with IBD, find some experts to grade IBD severity on the images, and train a CNN model using the images and expert labels.

In 2016, developing a CNN wasn't easy. There was no database of endoscopic images or simple methods for image labeling. The CNN needed tens of thousands of images. How were we to collect enough images with a broad range of IBD severity? I also reached some technical limits and needed help solving computational challenges.

Designing our first IBD endoscopic CNN took years of reading, coursework, additional training, and a new host of collaborators.

Failure was frequent, and my colleagues and I spent a lot of nights and weekends looking at thousands of individual endoscopic images. But we eventually had a working model for grading endoscopic severity, and its performance exceeded our expectations.

To our surprise, the CNN model grading of ulcerative colitis severity almost perfectly matched the opinion of IBD experts (JAMA Netw Open. 2019;2[5]:e193963). We introduced the proof of concept that AI could automate complex disease measurement for IBD.

What took us 3 years in 2016 would take about 3 weeks today.

You have said that AI could help reduce the substantial administrative burdens in medicine today. What might an AI-assisted future look like for time-strapped gastroenterologists?

We will be spending more time on complex decision-making and developing treatment plans, with less time needed to hunt for information in the chart and administrative tasks.

The practical applications of AI will chip away at tedious mechanical tasks, soon to be done by machines, reclaiming time for gastroenterologists.

For example, automated documentation is almost usable, and audio recordings in the clinic could be leveraged to generate office notes.

'Humans anticipate gaps in data and customize the weighting of information when making decisions for individuals. An experienced gastroenterologist can incorporate risks, harms, and costs in ways AI is several generations from achieving.'

Computer vision analysis of endoscopic video is generating draft procedural notes and letters to patients in a shared language, as well as recommending surveillance intervals based on the findings.

Text processing is already being used to automate billing and manage health maintenance like vaccinations, laboratory screening, and therapeutic drug monitoring.

Unfortunately, I don't think that AI will immediately help with burnout. These near-term AI administrative assistant advantages, however, will help us manage the increasing patient load, address physician shortages, and potentially improve access to care in underserved areas.

Were there any surprises in your work?

I must admit, I was certain AI would put us gastroenterologists to shame. Over time, I have reversed that view.

AI really struggles to understand the holistic patient context when interpreting disease and predicting what to do for an individual patient. Humans anticipate gaps in data and customize the weighting of information when making decisions for individuals. An experienced gastroenterologist can incorporate risks, harms, and costs in ways AI is several generations from achieving.

With certainty, AI will outperform gastroenterologists for tedious and repetitive tasks, and we should gladly expect AI to assume those responsibilities. However, many unknowns remain in the daily management of GI conditions. We will continue to rely on the clinical experience, creativity, and improvisation of gastroenterologists for years to come.

Has there been a turning-point moment when it felt like this technology moved from being more theoretical to something with real-world clinical applications?

Last spring, I saw a lecture by Peter Lee, who is president of Microsoft Research and a leader in developing AI-powered applications in medicine and scientific research, demonstrating how a large language model (LLM) could "understand" medical text and generate responses to questions. My jaw dropped.

We watched an LLM answer American Board of Internal Medicine questions with perfect explanations and rationale. He demonstrated how an audio recording of a clinic visit could be used to automatically generate a SOAP (subjective, objective assessment and plan) note. It was better than anything I would have drafted. He also showed how the LLM could directly ingest EHR data, without any modification, and provide a great diagnosis and treatment plan. Finally, LLM chatbots could carry on an interactive conversation with a patient that would be difficult to distinguish from a human physician.

The inevitability of AI-powered transformations in gastroenterology care became apparent.

Documentation, billing, and administrative work will be handled by AI. AI will collect and organize information for me. Chart reviews and even telephone/email check-ups on patients will be a thing of the past. AI chatbots will be able to discuss an individual patient's condition and test results. Our GI-AI assistants will proactively collect information from patients after hospitalization or react to a change in labs.

AI will soon be an amazing diagnostician and will know more than me. So do we need to polish our

Continued on following page

Ustekinumab Biosimilar Otulfi Approved in US

BY LUCY HICKS

The Food and Drug Administration has approved ustekinumab-aauz (Otulfi), a biosimilar that references Johnson & Johnson's ustekinumab (Stelara).

This is the fourth ustekinumab biosimilar approved in the United States. Like the reference product, ustekinumab-aauz is indicated for

- Patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- Patients 6 years or older with active psoriatic arthritis
- Adult patients with moderately to severely active Crohn's disease
- Adult patients with moderately to severely active ulcerative colitis

Ustekinumab-aauz, produced by a partnership between Fresenius Kabi and Formycon, has two formulations: subcutaneous injection (45-mg/0.5-mL or 90-mg/mL solution in a single-dose prefilled syringe) or intravenous infusion (130-mg/26-mL solution in a single-dose vial).

Ustekinumab-aauz has two formulations: subcutaneous injection (45-mg/0.5-mL or 90-mg/mL solution in a single-dose prefilled syringe) or intravenous infusion (130-mg/26-mL solution in a single-dose vial).

The biosimilar will launch in the United States "no later than February 22, 2025," according to the press release, "in accordance with the patent settlement between Fresenius Kabi, Formycon, and Johnson & Johnson."

Ustekinumab-aauz is Fresenius Kabi's fourth biosimilar granted US approval, behind adalimumab-aacf (Idacio), tocilizumab-aazg (Tyenne), and pegfilgrastim-fpgk (Stimufend). ■

Continued from previous page

resumes for new careers? No, but we will need to adapt to changes, which I believe on the whole will be better for gastroenterologists and patients.

What does adaptation look like for gastroenterologists over the next handful of years?

Like any other tool, gastroenterologists will be figuring out how to use AI prediction models, chatbots, and imaging analytics. Value, ease of use, and information-gain will drive which AI tools are ultimately adopted.

Memory, information recall, calculations, and repetitive tasks where gastroenterologists occasionally make errors or find tiresome will become the job of machines. We will still be the magicians, now aided by machines, applying our human strengths of contextual awareness, judgment, and creativity to find customized solutions for more patients.

That, I think, is the future that we are reliably moving toward over the next decade — a human-computer cooperative throughout gastroenterology (including IBD) and, frankly, all of medicine. ■

Time-Restricted Eating Fails for Weight Loss and Glucose Homeostasis

BY DIANA SWIFT

In the setting of isocaloric eating, time-restricted eating (TRE) did not reduce weight or improve glucose homeostasis relative to a usual eating pattern, a small randomized controlled trial found.

The results suggested that any effects of TRE on weight observed in prior studies may be due to reductions in caloric intake and not timing,

Dr. Pilla

'Our findings suggest that if or when TRE interventions induce weight loss, it is likely in part due to a reduction in energy intake, and therefore, clinicians can counsel patients that TRE may help them lose weight.'

according to Nisa M. Maruthur, MD, MHS, of the Division of General Internal Medicine at Johns Hopkins School of Medicine in Baltimore, Maryland, and colleagues.

Published in *Annals of Internal Medicine* (2024 Apr 19. doi: 10.7326/M23-313), the 12-week trial randomly assigned 41 adults aged 18-69 years with obesity and prediabetes or diet-controlled diabetes 1:1 as follows: to TRE, involving a 10-hour eating window with 80% of calories consumed before 1 PM, or to usual eating pattern, involving a ≤ 16-hour window, with at least 50% of calories consumed after 5 PM. The regimen in each group was based on the OmniHeart unsaturated fat diet and the SPICE study.

Dr. Varady

'Many patients stop following standard-care diets (such as daily calorie restriction) because they become frustrated with having to monitor food intake vigilantly each day.'

"The diet was similar to the DASH [Dietary Approaches to Stop Hypertension] diet for hypertension and maybe a bit higher in unsaturated fat and micronutrients," said study co-author Scott J. Pilla, MD, MHS, an assistant professor of medicine at Johns Hopkins Bloomberg School of Public Health, Baltimore, in an interview. For each participant, macro- and micronutrient content remained constant throughout the study period, with total calories individually determined at baseline and ranging from 1600 to 3500 kcal/d. "That differs from some TRE studies in which calories were adjusted according to whether participants lost or gained weight," he said. "This was a purely mechanistic study to determine the impact of time of eating alone with no change in calories."

Although the current findings revealed no weight loss advantage, some evidence suggests that limiting the food consumption window to 4-10 hours naturally reduces energy intake by approximately 200-550 calories per day and can result in a loss of 3%-5% of baseline body weight for 2-12 months. In addition, TRE has been shown to improve metabolic risk factors, such as insulin resistance, blood pressure, and triglyceride concentrations — but not in this study.

The Cohort

The mean age was 59 years, 93% of patients were women, and 93% were Black. The mean body mass index was 36, and the mean baseline weight was 96.2 kg — 95.6 kg in the TRE group and 103.7 kg in the usual eating–pattern group.

At 12 weeks, weight decreased comparably by 2.3 kg (95% CI, 1.0-3.5) in the TRE group and by 2.6 kg (95% CI, 1.5-3.7) in the usual eating–pattern group. Change in glycemic measures did not differ between the two groups.

Interestingly, self-reporting questionnaires revealed a slight reduction in physical activity in the TRE group, an effect that requires further study. "We don't know why but anecdotally, some TRE participants said they tended to go to bed earlier," Dr. Pilla said. Earlier bedtimes may put an end sooner to the daily eating pattern.

Subanalyses of the data are ongoing and will be published later.

"In the context of several clinical trials that suggest a benefit of TRE, our findings suggest that if or when TRE interventions induce weight loss, it is likely in part due to a reduction in energy intake, and therefore, clinicians can counsel patients that TRE may help them lose weight by decreasing their caloric intake," the authors wrote.

In an accompanying editorial, Krista A. Varady, PhD, and Vanessa M. Oddo, PhD, of the Department of Kinesiology and Nutrition at the University of Illinois–Chicago, said the study results have important clinical implications. "Many patients stop following standard-care diets (such as daily calorie restriction) because they become frustrated with having to monitor food intake vigilantly each day," they wrote.

Although TRE is no more effective than other diet interventions for weight reduction, it offers a simplified approach to treat obesity by omitting the need for calorie counting. "TRE bypasses this requirement simply by allowing participants to 'watch the clock' instead of monitoring calories, while still producing weight loss," they wrote.

The straightforward nature of this diet makes it well suited for remote delivery, which can reduce the scheduling and financial barriers associated with inpatient visits, they added. "Moreover, TRE does not require the purchase of expensive food products and allows a person to continue consuming familiar foods, making it a high accessible diet for lower-resource populations."

Gastroenterologists and Obesity

Of late, support has grown for gastroenterologists to become actively involved in obesity treatment — even to "take ownership" of this field.

In a 2023 article in *Gut*, Michael Camilleri, MD, DSC, AGAF, a gastroenterologist at the Mayo Clinic in Rochester, Minnesota, made the case for the natural fit between gastrointestinal (GI) specialists and obesity management. He noted that obesity is a significant risk factor for GI, pancreatic, and liver diseases. It can even affect inflammatory bowel disease.

"Treating obesity starting when patients present in gastroenterology and hepatology clinics has potential to impact serious consequences of obesity such as cardiovascular risks," he wrote.

Gastroenterologists already treat GI conditions with pharmacologic and surgical interventions that can also be used to treat obesity and improve glycemic control. These include pancreatic lipase inhibitors and incretin, bariatric endoscopy and surgery, and combination therapies targeting metabolic problems.

This study was supported by the American Heart Association.

Dr. Camilleri

'Treating obesity starting when patients present in gastroenterology and hepatology clinics has potential to impact serious consequences of obesity such as cardiovascular risks.'

Dr. Maruthur reported receiving royalties from a virtual diabetes prevention program. Dr. Pilla reported receiving travel, advisory, and speaker fees from the American Diabetes Association. Numerous authors reported receiving grants from government and nonprofit research funding organizations. Dr. Varady disclosed having no competing interests. Dr. Odda reported receiving research support and honoraria from government nonprofit funding organizations. ■

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Prescribing Recommendations

Resmetirom *from page 1*

benchmarks from published literature, and conducted a post hoc analysis of phase 3 MASTERO-NASH trial data. Trial enrollment required at least three cardiometabolic risk factors and a vibration-controlled transient elastography (VCTE) prescreening within the past 3 months. The population included 888 patients with F2 or F3 disease.

Recommendations were split into three categories: treat with resmetirom, consider treating with resmetirom, and do not treat with resmetirom.

The recommendation to treat calls for a VCTE of 10-15 kPa, a magnetic resonance elastography (MRE) of 3.3-4.2 kPa, or an Enhanced Liver Fibrosis (ELF) score of 9.2-10.4, with the caveat that an ELF score below 9.8 requires a second NIT for confirmation. Alternatively, a positive composite score such as FibroScan–aspartate aminotransferase (FAST), MRI–AST (MAST), or MRE + Fibrosis-4 (MEFIB) may serve as grounds for treatment. For any of the previous, platelets must concurrently be at least 140 with no evidence of portal hypertension.

The recommendation to consider treatment depends upon a VCTE of 15.1-19.9 kPa, an MRE of 4.3-4.9 kPa, an ELF score of 10.5-11.3, or positive FAST, MAST, or MEFIB. Again, these require a concurrent platelet count of 140 and no portal hypertension.

Finally, patients should not be treated with resmetirom if they have a VCTE of 20 kPa or greater, an MRE of 5 kPa or greater, and an ELF score greater than 11.3.

Noureddin and colleagues also offered guidance on monitoring strategies, including follow-up at 3, 6, and 12 months.

The approval of resmetirom as the first registered treatment for metabolic dysfunction–associated steatohepatitis (MASH) marks a historic moment. This expert panel recommendation document offers valuable guidance on selecting patients for resmetirom treatment, monitoring responses, and managing potential side effects and drug-drug interactions. It also highlights the complexities of applying noninvasive tests for treatment initiation. Clinicians must identify MASH patients with significant or advanced fibrosis while avoiding those with cirrhosis and hepatic decompensation. Management will be simplified if the MAESTRO-OUTCOMES trial confirms that resmetirom is safe and effective for patients with compensated MASH cirrhosis.

Dr. Wong

Notably, the recommended noninvasive test cutoffs are partly based on the MAESTRO-NASH trial results. Because the trial enrolled patients using specific noninvasive tests, it represents an enriched cohort, potentially skewing test performance, compared with regular clinical settings. Additionally, the high cost of the drug might lead to restricting treatment to patients with more advanced fibrosis, resulting in proposed cutoffs that lean toward advanced fibrosis rather than significant fibrosis. As more treatments for MASH emerge in the coming years, drug costs may decrease, warranting a reassessment of these cutoffs.

The most reliable response biomarkers in the MAESTRO-NASH trial include reductions in MRI–proton density fat fraction (MRI-PDFF) and serum alanine aminotransferase, despite MRI-PDFF being limited by cost and availability. Worsening liver stiffness measurement via vibration-controlled transient elastography is suggested as a stopping rule, although this is not supported by resmetirom trial data. Short-term increases in liver stiffness may yield false positives, so it is advisable to repeat or use alternative noninvasive tests before discontinuing treatment.

Vincent Wai-Sun Wong, MD, is Mok Hing Yiu Professor of Medicine at the Chinese University of Hong Kong, China. He reported his role as a consultant or advisory board member for AbbVie, AstraZeneca, Boehringer Ingelheim, Echosens, Eli Lilly, Gilead Sciences, Intercept, Inventiva, Merck, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, and Visirna; and a speaker for Abbott, AbbVie, Echosens, Gilead Sciences, Novo Nordisk, and Unilab. He has received a research grant from Gilead Sciences, and is the cofounder of Illuminatio Medical Technology.

At 3 months, the focus should be safety, including screening for drug-related liver injury and other adverse events that warrant cessation.

At 6 months, alanine aminotransferase (ALT) levels, VCTE, or MRI–proton density fat fraction (PDFF) tests can indicate early response, but treatment should generally continue regardless of results.

At 12 months, efficacy can be fully evaluated. ALT normalization, or improvement of more than 17 IU/L or more than 20%, along with a 30% or greater drop in VCTE, or at least 30% drop in liver fat on MRI-PDFF, serve as grounds for continuation.

Noureddin and colleagues noted that ALT improvement should be paired with corresponding improvements in imaging, such as a 30% reduction in MRI-PDFF. Even if ALT levels do not improve, a 30% or greater reduction in MRI-PDFF can still indicate a positive response; however, VCTE alone may not be sufficient to fully assess treatment response.

"Emerging data, particularly regarding the noninvasive assessment of treatment response, are likely to further modify patient selection, safety signals, and efficacy algorithms," they concluded.

This study was supported by the National Center for Advancing Translational Sciences, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Heart, Lung, and Blood Institute, the John C. Martin Foundation, and the National Institute on Alcohol Abuse and Alcoholism. The investigators disclosed additional relationships with Novo Nordisk, Pfizer, Shire, and others. ■

Common Crohn's Immune Response to Gut Bacteria Suggests Therapeutic Target

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

Many patients with Crohn's disease (CD) have a heightened immune response to flagellins expressed by commensal gut bacteria *Lachnospiraceae*, with seroreactivity appearing up to 5 years prior to development of Crohn's complications, according to investigators.

These findings suggest that the flagellin cytometric bead array used in the present study could serve as a simple diagnostic and prognostic tool for patients with CD, and point to a new therapeutic target, lead author Qing Zhao, MD, PhD, of the University of Alabama at Birmingham, and colleagues reported.

Dr. Zhao

Previously, Zhao and colleagues found that about 30% of patients with CD had elevated IgG responses to multiple *Lachnospiraceae* flagellins, and stronger reactivity was associated with higher flagellin-specific CD4+ T cells in circulation.

"In this study, we aimed to identify immunodominant B cell peptide epitopes shared among *Lachnospiraceae* bacterial flagellins in patients with CD and to correlate this immune reactivity with the clinical disease course," the investigators wrote in *Gastroenterology* (2024 Aug. doi: 10.1053/j.gastro.2024.08.015).

To this end, the investigators analyzed serum samples from adult CD patients, pediatric CD patients, and healthy infants without inflammatory bowel disease, with data derived from multiple

Continued on following page

Liquid Fasting For 24 Hours Pre-Surgery Mitigates Negative Impact of Semaglutide

BY WILL PASS
MDedge News

FROM TECHNIQUES AND INNOVATIONS IN GASTROINTESTINAL ENDOSCOPY

Semaglutide use is associated with an increased risk of retained solid gastric contents, but colonoscopy prep appears to mitigate this issue, according to investigators.

These findings suggest that patients taking glucagon-like peptide 1 receptor agonists (GLP-1RAs) may benefit from a 24-hour liquid fast before anesthetic procedures without the need for a medication hold, reported lead author Haarika Korlipara, MD, of NewYork–Presbyterian/Weill Cornell Medical Center, New York City, and colleagues.

"[T]he effects of delayed gastric emptying in patients on long-acting GLP-1RAs are clinically important in the management of anesthetized patients, who may develop periprocedural complications in the setting of retained solid gastric contents," the investigators wrote in *Techniques and Innovations in Gastrointestinal Endoscopy* (2024 Aug. doi: 10.1016/j.tige.2024.07.001).

The researchers retrospectively analyzed clinical data from 1,212 patients undergoing upper endoscopy at a tertiary care center. Among them, 602 were on semaglutide for more than 4 weeks, while 610 were controls not taking the medication.

The primary outcome was the presence of retained solid gastric contents. Secondary outcomes included the need for intubation, early procedure termination, and recommendations for repeat endoscopy.

'[T]he effects of delayed gastric emptying in patients on long-acting GLP-1RAs are clinically important in the management of anesthetized patients, who may develop periprocedural complications in the setting of retained solid gastric contents.'

Semaglutide use was an independent predictor of retained solid gastric contents (odds ratio [OR], 4.74; 95% CI, 2.40-9.35; *P* less than .0001). Multivariable propensity-matched analysis showed a 6% absolute increase in retained gastric contents in the semaglutide group compared to controls (*P* less than .0001).

This increase appeared clinically relevant, as semaglutide use was associated with a higher rate of early procedure termination (OR, 3.09; *P* = 0.02) and recommendations for repeat endoscopies (OR, 3.61; *P* = 0.02), "indicating the degree of retained solid gastric contents was enough to limit the intended gastric mucosal examination," the investigators wrote.

However, patients who underwent same-day colonoscopy, which included a 24-hour clear liquid fast leading up to the procedure, were less likely to have retained gastric contents (OR, 0.41; 95% CI, 0.23-0.73; *P* = 0.003), suggesting that extended fasting protocols may mitigate the risk of procedural complications.

"Patients with a history of gastroparesis are often advised to stop ingesting solid foods and maintain a clear liquid diet for a longer period than standard [American Society of Anesthesiologists] guidance before anesthetized procedures," Korlipara and colleagues wrote. "In our opinion, this recommendation should be considered in patients on long-term GLP-1RA therapy, in response to the findings reported in this study and others about the protective effects of a 24-hour liquid fast."

Point-of-care gastric ultrasound may also be considered to evaluate patients at higher risk of retained stomach contents, they added, especially in patients with additional risk factors for delayed gastric emptying.

"Previously published data have linked prolonged gastric emptying delays in patients chronically using these medications," they wrote. "Considering the effect on blood sugar and associated procedural risk, especially in patients taking this medication for diabetes management, more studies are warranted to determine the effect of medication on periprocedural complications and recommend repeat evaluation."

After this study was released, new clinical guidance on the use of GLP-1RAs before surgery was co-published by AGA and four other societies (Clin Gastroenterol Hepatol. 2024 Oct. doi: 10.1016/j.cgh.2024.10.003). The guidance notes that, in most cases, patients can continue to take GLP-1RAs, but individual risk factors for complications should be assessed prior to surgery. The guidance cautions that patients at high risk for significant GI side effects should follow a liquid diet for 24 hours before a procedure and the anesthesia plan be adjusted accordingly. In rare cases, the procedure should be delayed.

Dr. Korlipara disclosed no conflicts of interest. ■

Continued from previous page

sources. Adult patients with CD were part of a regional cohort recruited at the University of Alabama at Birmingham, while pediatric patients with CD came from the RISK Stratification Study, a multisite cohort study across the United States and Canada. Samples from healthy infants were collected from three diverse geographic locations: Uganda, Sweden, and the United States, providing a broad comparison of immune responses to *Lachnospiraceae* flagellin across populations.

Samples were analyzed via two main methods: a flagellin peptide microarray and a cytometric bead array. The microarray, comprising sequential *Lachnospiraceae*-derived peptides, enabled identification of IgG responses specific to individual bacterial peptides. The cytometric bead array allowed for multiplexed detection of IgG, IgA, and IgM antibodies to these peptides, quantifying immune reactivity and enabling correlation with clinical disease data.

This approach revealed that nearly half of patients with CD — both adults and children — had a strong IgG immune response targeting a specific bacterial peptide in the *Lachnospiraceae* flagellin hinge region. This response was linked to an increased risk of disease complications over time, suggesting the peptide's potential as a biomarker for CD severity and progression, according to the investigators.

Of note, healthy infants also exhibited an elevated IgG response to the same bacterial peptide at around 1 year of age, but this response declined as they grew older, in contrast to its persistence in CD patients. This difference points to a possible failure in immune tolerance in CD, where the natural immune response to gut bacteria in infancy may become dysregulated, Zhao and colleagues explained.

'We aimed to identify immunodominant B cell peptide epitopes shared among *Lachnospiraceae* bacterial flagellins in patients with CD and to correlate this immune reactivity with the clinical disease course.'

"The flagellin cytometric bead array used in this study holds potential for a simplified yet robust diagnostic and prognostic assay for Crohn's disease," they concluded. "Given that reactivity to the dominant flagellin epitope is strongly associated with the development of disease complications, this technique may also assist in identifying patients with Crohn's disease who would benefit from early therapy."

Zhao and colleagues also called for future studies to characterize the role of flagellin hinge peptide–specific IgG antibodies in CD pathogenesis, and to explore the hinge peptide as a potential therapeutic target.

The study was supported by a Synergy Award from the Kenneth Rainin Foundation, a Career Development Award from the Crohn's and Colitis Foundation, and grants from the Department of Veterans Affairs, National Institute of Allergy and Infectious Diseases, National Institutes of Health, and National Institute of Diabetes and Digestive and Kidney Diseases. One coauthor and the University of Alabama at Birmingham hold a patent on *Lachnospiraceae* A4 Fla2, licensed for clinical application by Prometheus Laboratories. Four study coauthors have filed a patent for the flagellin peptide cytometric bead array. One coauthor serves as the founder and chief scientific officer of ImmPrev Bio, a company developing an antigen-directed immunotherapy for Crohn's disease. ■

Medical, Endoscopic, and Surgical Management of Gastroesophageal Reflux Disease

BY PATRICK CHANG, MD; SUPISARA TINTARA, MD; AND JENNIFER PHAN, MD

Dr. Chang, Dr. Tintara, and **Dr. Phan** are based in the Division of Gastrointestinal and Liver Disease at the University of Southern California in Los Angeles. They have no conflicts of interest to declare.

Introduction

Gastroesophageal reflux disease (GERD) is a frequently encountered condition, and rising annually.[1] A recent meta-analysis suggests nearly 14% (1.03 billion) of the population is affected worldwide. Differences may range by region from 12% in Latin America to 20% in North America, and by country from 4% in China to 23% in Turkey.[1] In the United States, 21% of the population is afflicted with weekly GERD symptoms.[2] Novel medical therapies and endoscopic options provide clinicians with opportunities to help patients with GERD.[3] Herein, we review diagnostics as well as the evolution of medical, endoscopic, and basic surgical management for GERD.

Diagnosis

Definition

GERD was originally defined by the Montreal consensus as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[4] Heartburn and regurgitation are common symptoms of GERD, with a sensitivity of 30%-76% and specificity of 62%-96% for erosive esophagitis (EE), which occurs when the reflux of stomach content causes esophageal mucosal breaks.[5] The presence of characteristic mucosal injury observed during an upper endoscopy or abnormal esophageal acid exposure on ambulatory reflux monitoring are objective evidence of GERD. A trial of a proton pump inhibitor (PPI) may function as a diagnostic test for patients exhibiting the typical symptoms of GERD without any alarm symptoms.[3,6]

Endoscopic Evaluation and Confirmation

The 2022 American Gastroenterological Association (AGA) clinical practice update recommends diagnostic endoscopy, after PPIs are stopped for 2-4 weeks, in patients whose GERD symptoms do not respond adequately to an empiric trial of a PPI.[3] Those with GERD and alarm symptoms such as dysphagia, weight loss, bleeding, and vomiting should undergo endoscopy as soon as possible. Endoscopic findings of EE (Los Angeles [LA] Grade B or more severe) and long-segment Barrett's esophagus (> 3-cm segment with intestinal metaplasia on biopsy) are diagnostic of GERD.[3]

Reflux Monitoring

With ambulatory reflux monitoring (pH or impedance-pH), esophageal acid exposure (or neutral refluxate in impedance testing) can be measured to confirm GERD diagnosis and to correlate symptoms with reflux episodes. Patients with atypical GERD symptoms or patients with a confirmed diagnosis of GERD whose symptoms have not improved sufficiently with twice-daily PPI therapy should have esophageal impedance-pH monitoring while on PPIs.[6,7]

Esophageal Manometry

High-resolution esophageal manometry can be used to assess motility abnormalities associated with GERD.

Although no manometric abnormality is unique to GERD, weak lower esophageal sphincter (LES) resting pressure and ineffective esophageal motility frequently coexist with severe GERD.[6]

Manometry is particularly useful in patients considering surgical or endoscopic anti-reflux procedures to evaluate for achalasia,[3] an important contraindication to surgery.

Medical Management

Management of GERD requires a multidisciplinary and personalized approach based on symptom presentation, body mass index, endoscopic findings (eg, presence of EE, Barrett's esophagus, hiatal hernia), and physiological abnormalities (eg, gastroparesis or ineffective motility).[3]

Lifestyle Modifications

Recommended lifestyle modifications include weight loss for patients with obesity, stress reduction, tobacco and alcohol cessation, elevating the head of the bed, staying upright during and after meals, avoidance of food intake < 3 hours before bedtime, and cessation of foods that potentially aggravate reflux symptoms such as coffee, chocolate, carbonated beverages, spicy foods, acidic foods, and foods with high fat content.[6,8]

Medications

Pharmacologic therapy for GERD includes medications that primarily aim to neutralize or reduce gastric acid — we summarize options in Table 1.[3,8]

Proton Pump Inhibitors

Most guidelines suggest a trial of 4-8 weeks of once-daily enteric-coated PPI before meals in patients with typical GERD symptoms and no alarm symptoms. Escalation to double-dose PPI may be considered in the case of persistent symptoms. The relative potencies of standard-dose pantoprazole, lansoprazole, esomeprazole, and rabeprazole are presented in Table 1.[9] When a PPI switch is needed, rabeprazole may be considered as it is a PPI that does not rely on CYP2C19 for primary metabolism.[9]

Acid suppression should be weaned down to the lowest effective dose or converted to H2 receptor agonists (H2RAs) or other antacids once symptoms are sufficiently controlled unless patients have EE, Barrett's esophagus, or peptic stricture.[3] Patients with severe GERD may require long-term PPI therapy or an invasive anti-reflux procedure.

Recent studies have shown that potassium–competitive acid blockers (PCAB) like vonoprazan may offer more effective gastric acid inhibition. While not included in the latest clinical practice update, vonoprazan is thought to be superior to lansoprazole for those with

Gastroesophageal reflux disease (GERD) is a common referral to gastroenterology, and endoscopic management of GERD is a growing field. Dr. Patrick Chang, Dr. Supisara Tintara, and Dr. Jennifer Phan of the University of Southern California review diagnostic modalities and treatment of GERD.

The authors discuss medical management and when to refer for endoscopic and surgical evaluation. They expand on the literature behind endoscopic treatments, including transoral incisionless fundoplication (TIF), Stretta, anti-reflux mucosectomy (ARM), mucosal ablation and suturing of the EG junction (MASE), and resection and plication (RAP), as well as surgical options and outcomes.

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

Table 1: Options for Medical Management of GERD

Treatments	Starting dose (OE**)	Maximal dose (OE)
Proton pump inhibitor		
Pantoprazole	40 mg once daily (9)	40 mg twice daily (18)
Lansoprazole	15 mg once daily (13.5)	30 mg twice daily (54)
Omeprazole	20 mg once daily (20)	40 mg twice daily (80)
Esomeprazole	20 mg once daily (32)	40 mg twice daily (128)
Dexlansoprazole	30 mg once daily (n/a)	60 mg once daily (n/a)
Rabeprazole	20 mg once daily (36)	20 mg twice daily (72)
Potassium–competitive acid blocker		
Vonoprazan	20 mg once daily (120)	20 mg twice daily (240)
Adjunctive therapy*	**Examples**	
H2 receptor antagonist	Famotidine, ranitidine	
Alginates	Gaviscon	
GABA-B agonist	Baclofen	
Prokinetics	Metoclopramide	
Behavioral therapies	Hypnotherapy, cognitive-behavioral therapy, diaphragmatic breathing, relaxation strategies	

*Requires personalization and discussion with patients on benefits and risks as contemporary guidance may vary;
**OE: Omeprazole equivalence: adjusted to omeprazole 40 mg each day of therapy[9,10]

LA Grade C/D esophagitis for both symptom relief and healing at 2 weeks.[10]

Adjunctive Therapies

Alginates can function as a physical barrier to even neutral reflux and may be helpful for patients with postprandial or nighttime symptoms as well as those with hiatal hernia.[3] H2RAs can also help mitigate nighttime symptoms.[3] Baclofen is a gamma-aminobutyric acid–B agonist which inhibits transient lower esophageal sphincter relaxation (TLESR) and may be effective for patients with belching.[3] Prokinetics may be helpful for GERD with concomitant gastroparesis.[3] Sucralfate is a mucosal protective agent, but there is a lack of data supporting its efficacy in GERD treatment. Consider referral to a behavioral therapist for supplemental therapies, hypnotherapy, cognitive-behavior therapy, diaphragmatic breathing, and relaxation strategies for functional heartburn or reflux-associated esophageal hypervigilance or reflux hypersensitivity.[3]

When to Refer to Higher Level of Care

For patients who do not wish to remain on longer-term pharmacologic therapy or would benefit from anatomic repair, clinicians should have a discussion of risks and benefits prior to a consideration of referral for anti-reflux procedures.[3,6,8] We advise this conversation should include review of patient health status, postsurgical side effects such as increased flatus, bloating, and dysphagia as well as the potential need to still resume PPI post operation.[8]

Endoscopic Management

Patient Selection and Evaluation

For the groups indicated for a higher level of care, we agree with AGA recommendations, multi-society guidelines, and expert review,[3,7,11,12] and highlight potential options in Table 2. Step-up options should be based on patient characteristics and reviewed carefully with patients. Endoscopic therapies are less invasive than surgery and may be considered for those who do not require anatomic repair of hiatal hernia, do not want surgery, or are not suitable for surgery.

The pathophysiology of GERD is from a loss of the anti-reflux barrier of the esophageal gastric junction (EGJ) at the LES leading to unintended retrograde movement of gastric contents.[6] Anatomically, the LES is composed of muscles of the distal esophagus and sling fibers of the proximal stomach, the "external valve" from the diaphragmatic crura, and the "internal valve" from the gastroesophageal flap valve (GEFV). GERD occurs from mechanical failure of the LES. First, there may be disproportional dilation of the diaphragmatic crura as categorized by Hill Grade of the GEFV as seen by a retroflexed view of EGJ after 30-45 seconds of insufflation.[13] Second, there may be a migration of the LES away from the diaphragmatic crura as in the case of a hiatal hernia. Provocative maneuvers may reveal a sliding hernia by gentle retraction of the endoscope while under retroflexed view.[13] Third, there may be more frequent TLESR associated with GERD.[12]

The aim of most interventions is to restore competency of the LES by reconstruction of the GEFV via suture or staple-based approximation of tissue.[11,12] Intraluminal therapy may target the GEFV only at the internal valve. Therefore, most endoscopic interventions are limited to patients with intact diaphragmatic crura (ie, small to no hiatal hernia and GEFV Hill Grade 1 to 2). Contraindications for endoscopic therapy are moderate to severe reflux (ie, LA Grade C/ D), hiatus hernia 2 cm or larger, strictures, or long-segment Barrett's esophagus.

Utility, Safety, and Outcomes of TIF

Historically, endoscopic therapy targeting endoscopic fundoplication started with endoluminal gastro-gastric fundoplication (2005) which was a proof of concept of safe manipulation and suture for gastro-gastric plication to below the Z-line. Transoral incisionless fundoplication (TIF) 1.0 was suggested in 2007 for clinical application by proposing a longitudinal oriented esophago-gastric plication 1 cm above the Z-line.

In 2009, TIF 2.0 was proposed as a rotational 270° wrap of the cardia and fundus to a full-thickness esophago-gastric fundoplication around 2-4 cm of the distal esophagus. Like a surgical fundoplication, this reinforces sling fibers, increases the Angle of His and improves the cardiac notch. TIF 2.0 is indicated for those with small (< 2 cm) or no hiatal hernia and a

Continued on following page

Table 2: Summary of Endoscopic and Surgical Options With Estimated Post-Treatment PPI Daily Rates and Adverse Events (AE)

Therapy	Estimated rate of post-treatment daily PPI usage at time interval	Adverse events
Transoral incisionless fundoplication (TIF)	17% and 34% at 1 and 5 years	Severe AE < 1%, mild to moderate AE include chest pain, sore throat, dysphagia, bloating
Combination TIF with hiatal hernia repair	24% at 1 year	Severe AE < 1%, added risk of surgical hernia repair
Nonablative radiofrequency (Stretta)	49% at pooled follow-up	Severe AE < 1%, mild to moderate AE include bloating
Anti-reflux mucosectomy (ARM)	26% at 1 year	Overall AE rate: 16%
ARM with band ligation	45% at 6 months, pooled rate 65%	Overall AE rate: 21%
Roux-en-Y gastric bypass (RYGB)	48% at pooled interval (27-61 months)	Severe AE 8%-20%, postsurgical and mild AE include dumping syndrome and malabsorption
Magnetic sphincter augmentation	13% at 1 year	Severe AE 7.8%, requiring dilation, dysphagia, esophageal erosion, device erosion/migration
Laparoscopic Nissen fundoplication (LNF 360°)	30% at pooled interval (60-240 months)	Severe AE 10%, mild AE include dysphagia and gas bloat syndrome
Laparoscopic Toupet fundoplication (270°)	44% at pooled interval (60-240 months)	Severe AE 10%, lower risk of long-term dysphagia, gas bloat syndrome, bloating compared to LNF

Continued from previous page

GEFV Hill Grade 1 or 2. The present iteration of TIF 2.0 uses EsophyX-Z (EndoGastric Solutions; Redmond, Washington) which features dual-fastener deployment and a simplified firing mechanism. Plication is secured via nonresorbable polypropylene T-fasteners with strength equivalence of 3-0 sutures.

Compared with the original, TIF 2.0 represents a decrease of severe adverse events from 2%-2.5% to 0.4%-1%.[11,14] Based on longitudinal TEMPO data, patient satisfaction ranges between 70% and 90% and rates of patients reverting to daily PPI use are 17% and 34% at 1 and 5 years. A 5% reintervention rate was noted to be comparable with surgical reoperation for fundoplication.[15] One retrospective evaluation of patients with failed TIF followed by successful combination with hiatal hernia repair (cTIF) noted that in all failures there was a documented underestimation of a much larger crura defect at time of index procedure.[16]

Chest pain is common post procedure and patients and collaborating providers should be counseled on the expected course. In our practice, we admit patients for at least 1 post-procedure day and consider scheduling symptom control medications for those with significant pain.

TIF 2.0 for Special Populations

Indications for TIF 2.0 continue to evolve. In 2017, concomitant TIF 2.0 with hiatal hernia repair (cTIF or HH-TIF) for hernia > 2 cm was accepted for expanded use. In one study, cTIF has been shown to have similar outcomes for postprocedural PPI use, dysphagia, wrap disruption, and hiatal hernia recurrence, compared with hiatal hernia repair paired with laparoscopic Nissen fundoplication with possibly shorter postadmission stay, serious adverse events, and bloating.[17] A cTIF may be performed in a single general anesthetic session typically with a surgical hiatal hernia repair followed by TIF 2.0.

Other Endoscopic Procedures

Several other endoscopic interventions have been proposed for GERD management. The following procedures are under continuous study and should be considered only by those with expertise.

Stretta

The Stretta device (Restech; Houston, Texas) was approved in 2000 for use of a radiofrequency (RF) generator and catheter applied to the squamocolumnar junction under irrigation. Ideal candidates for this nonablative procedure may include patients with confirmed GERD, low-grade EE, without Barrett's esophagus, small hiatal hernia, competent LES with pressure > 5 mm Hg. Meta-analysis has yielded conflicting results over its efficacy, compared with TIF 2.0, and recent multi-society guidance suggests fundoplication over Stretta.[7]

ARM, MASE, and RAP

Anti-reflux mucosectomy (ARM) has been proposed based on the observation that patients undergoing mucosectomy for neoplasms in the cardia had improvement of reflux symptoms.[11,12] Systematic review has suggested a clinical response of 80% of either PPI discontinuation or reduction, but 17% of adverse events include development of strictures. Iterations of ARM continue to be studied including ARM with band ligation and endoscopic submucosal dissection for GERD.[12]

Experts have proposed incorporating endoscopic suturing of the EGJ to modulate the LES. Mucosal ablation and suturing of the EG junction (MASE) has been proposed by first priming tissue via argon plasma coagulation (APC) prior to endoscopic overstitch of two to three interrupted sutures below the EGJ to narrow and elongate the EGJ. The resection and plication (RAP) procedure performs a mucosal resection prior to full-thickness plication of the LES and cardia.[11,12] Expert opinion has suggested that

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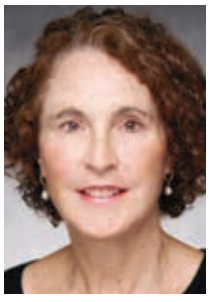
FIT Performance for CRC Screening Varies Widely

BY MEGAN BROOKS

Although considered a single class, fecal immunochemical tests (FITs) vary in their ability to detect advanced colorectal neoplasia (ACN) and should not be considered interchangeable, new research suggests.

In a comparative performance analysis of five commonly used FITs for colorectal cancer (CRC) screening, researchers found statistically significant differences in positivity rates, sensitivity, and specificity, as well as important differences in rates of unusable tests.


Dr. Levy


Dr. Smith

"Our findings have practical importance for FIT-based screening programs as these differences affect the need for repeated FIT, the yield of ACN detection, and the number of diagnostic colonoscopies that would be required to follow-up on abnormal findings," wrote the researchers, led by Barcey T. Levy, MD, PhD, of the University of Iowa, Iowa City.

The study was published in *Annals of Internal Medicine* (2024 Sept. doi: 10.7326/M24-0080).

Wide Variation Found

Despite widespread use of FITs for CRC screening, there are limited data to help guide test selection. Understanding the comparative performance of different FITs is "crucial" for a successful screening program, the researchers wrote.

Levy and colleagues directly compared the performance of five commercially available FITs — including four qualitative tests (Hemoccult ICT, Hemosure iFOB, OC-Light S FIT, and QuickVue iFOB) and one quantitative test (OC-Auto FIT) — using colonoscopy as the reference standard.

Participants included a diverse group of 3761 adults (mean age, 62 years; 63% women). Each participant was given all five tests and completed them using the same stool sample. They sent the tests by first-class mail to a central location, where FITs were analyzed by a trained professional on the day of receipt.

The primary outcome was test performance for ACN, defined as advanced polyps or CRC.

A total of 320 participants (8.5%) were found to have ACN based on colonoscopy results, including 9 with CRC (0.2%) — rates similar to those in other studies.

The sensitivity for detecting ACN ranged from 10.1% (Hemoccult ICT) to 36.7% (OC-Light S FIT), and specificity varied from 85.5% (OC-Light S FIT) to 96.6% (Hemoccult ICT).

"Given the variation in FIT cutoffs reported by manufacturers, it is not surprising that tests with lower cutoffs (such as OC-Light S FIT) had higher sensitivity than tests with higher cutoffs (such as Hemoccult ICT)," Levy and colleagues wrote.

Test positivity rates varied fourfold across FITs, from 3.9% for Hemoccult ICT to 16.4% for OC-Light S FIT.

The rates of tests deemed unevaluable (because of factors such as indeterminant results or user mistakes) ranged from 0.2% for OC-Auto FIT to 2.5% for QuickVue iFOB.

The highest positive predictive value (PPV) was observed with OC-Auto FIT (28.9%) and the lowest with Hemosure iFOB (18.2%). The negative predictive value was similar across tests, ranging from 92.2% to 93.3%, indicating consistent performance in ruling out disease.

The study also identified significant differences in test sensitivity based on factors such as the location of neoplasia (higher sensitivity for distal lesions) and patient characteristics (higher sensitivity in people with higher body mass index and lower income).

"Tests with lower sensitivity will miss more patients with CRC and advanced polyps, and tests with higher sensitivity and lower PPV will require more colonoscopies to detect patients with actionable findings," the authors wrote.

'Jaw-Dropping' Results

The sensitivity results are "jaw-dropping," said Robert Smith, PhD, senior vice-president for cancer screening at the American Cancer Society.

"What these numbers show is that the level that the manufacturers believe their test is performing is not reproduced," Smith added.

This study adds to "concerns that have been raised about the inherent limitations and the performance of these tests that … are supposed to be lifesaving," he said.

Clearance by the US Food and Drug Administration should mean that there's essentially "no risk to using the test in terms of the test itself being harmful," Smith said. But that's not the case with FITs "because it's harmful if you have cancer and your test doesn't find it."

The study had no commercial funding. Disclosures for authors are available with the original article. Smith had no relevant disclosures. ■

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RAP may be used in patients with altered anatomy whereas MASE may be used when resection is not possible (eg, prior scarring, resection, or ablation).[12]

Surgical Management

We agree with a recent multi-society guideline recommending an interdisciplinary consultation with surgery for indicated patients with refractory GERD and underlying hiatal hernia, or who do not want lifelong medical therapy.

Fundoplication creates a surgical wrap to reinforce the LES and may be performed laparoscopically. Contraindications include body mass index (BMI) > 35 kg/m^2 and significantly impaired dysmotility. Fundoplication of 180°, 270°, and 360° may achieve comparable outcomes, but a laparoscopic toupet fundoplication (LTF 270°) may have fewer postsurgical issues of dysphagia and bloating. Advantages for both anterior and posterior partial fundoplications have been demonstrated by network meta-analysis. Therefore, a multi-society guideline for GERD suggests partial over complete fundoplication.[7] Compared with posterior techniques, anterior fundoplication (Watson fundoplication) led to more recurrent reflux symptoms but less dysphagia and other side effects.[19]

Magnetic sphincter augmentation (MSA) is a surgical option that strengthens the LES with magnets to improve sphincter competence. In addition to listed contraindications of fundoplication, patients with an allergy to nickel and/or titanium are also contraindicated to receive MSA.[7] MSA has been suggested to be equivalent to LNF although there may be less gas bloat and greater ability to belch on follow-up.[20]

Surgical Options for Special Populations

Patients with medically refractory GERD and a BMI ≥ 35 kg/m^2 may benefit from either Roux-en-Y gastric bypass (RYGB) or fundoplication; however, sleeve gastrectomy is not advised.[7] In patients with BMI > 50 kg/m^2, RYGB may provide an optimal choice. We agree with consultation with a bariatric surgeon when reviewing these situations.

Conclusion

Patients with GERD are commonly encountered worldwide. Empiric PPI are effective mainstays for medical treatment of GERD. Novel PCABs (eg, vonoprazan) may present new options for GERD with LA Grade C/D EE and merit more study. In refractory cases or for patients who do not want long-term medical therapy, step-up therapy may be considered via endoscopic or surgical interventions. Patient anatomy and comorbidities should be considered by the clinician to inform treatment options. Surgery may have the most durable outcomes for those requiring step-up therapy. Improvements in technique, devices and patient selection have allowed TIF 2.0 to grow as a viable offering with excellent 5-year outcomes for indicated patients. ■

References

A complete list of references for this In Focus article is available on the GI & Hepatology News *website at www.MDedge.com/gihepnews.*

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