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GI&Hepatology News

March 2024

Volume 18 / Number 3

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Telephone Best for Switching Patient Colonoscopy Intervals

BY DIANA SWIFT

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Telephone outreach and secure messaging have better response rates than mailed letters when it comes to communicating updated colonoscopy intervals for patients with a history of low-risk adenomas, a randomized trial found.

In an article published in *Clinical Gastroenterology and Hepatology* (2024 Jan 6. doi: 10.1016/j.cgh.2023.12.027), a group led by Jeffrey K. Lee, MD, MPH, a gastroenterologist at Kaiser Permanente Medical Center in San Francisco, California, reported the following 60-day response rates for the three contact methods in potentially transitioning more than 600 post-polypectomy patients to the new interval:

- Telephone: 64.5%
- Secure messaging: 51.7%
- Mailed letter: 31.3%

Compared with letter outreach, overall rate differences were significant for telephone (18.1%) and secure message outreach (13.1%).

Such interventions are widely used, the authors noted (e.g., JAMA Intern Med. 2018 Dec.

See **Telephone** · *page 20*

Colorectal Cancer Risk Increasing Across Successive Birth Cohorts

CRC rates rising in younger generations, especially millennials.

BY CAROLYN CRIST

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Colorectal cancer (CRC) epidemiology is changing due to a birth cohort effect, also called birth cohort CRC — the observed phenomena of the rising risk for CRC across successive generations of people born in 1960 and later — according to a new narrative review.

Birth cohort CRC is associated with increasing rectal cancer (greater than colon cancer) diagnosis and distant-stage (greater than local-stage) CRC diagnosis, and a rising incidence of early-onset CRC (EO-CRC), defined as occurring before age 50.

Recognizing this birth cohort effect could improve the understanding of CRC risk factors, etiology, and mechanisms, as well as the public health consequences of rising rates.

"The changing epidemiology means that we need to redouble our efforts at optimizing early detection and prevention of colorectal cancer," Samir Gupta, MD, AGAF, the review's lead author and professor of gastroenterology at the University of California, San Diego, told *GI & Hepatology News*.

Dr. Gupta serves as the co-lead for the cancer control program at Moores Cancer Center at UC San Diego Health.

This requires "being alert for potential red flag

See **CRC risk** · *page 16*

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LETTER FROM THE EDITOR

Shining a Light on Colorectal Cancer

For more than two decades, March has been designated Colorectal Cancer Awareness Month. This annual observance serves as a reminder to spread the word in our local and national communities regarding the value of colorectal cancer screening and prevention. CRC prevention through screening and surveillance is a core part of our practice as gastroenterologists and plays a critical role in improving outcomes and reducing mortality from the second leading cause of cancer deaths in the US.

Dr. Adams

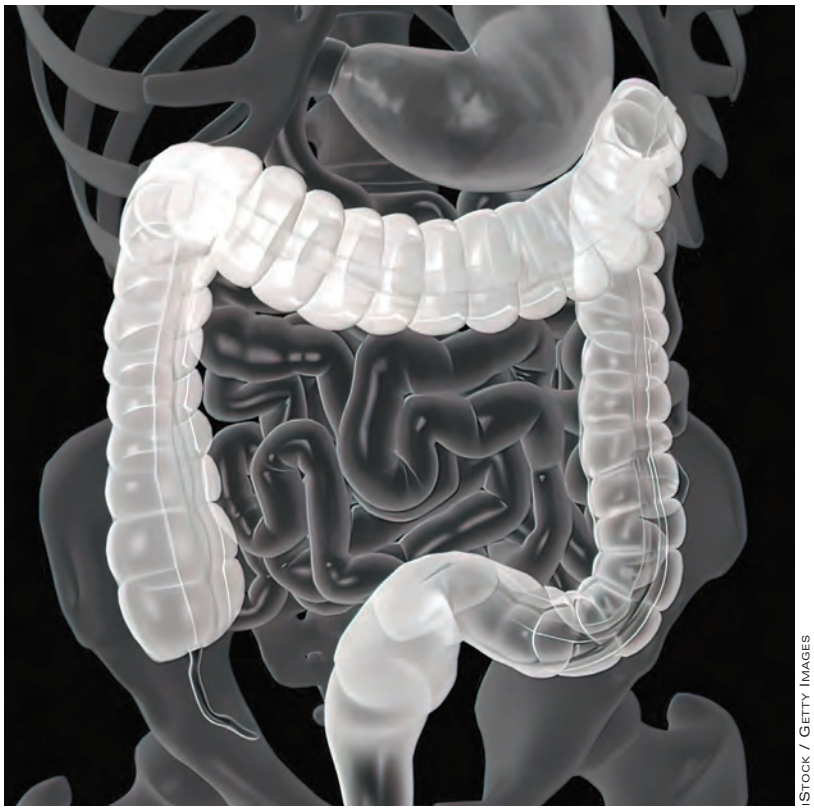
While we have made great strides in increasing awareness among patients of the need for screening, overall screening rates remain well below our national target of 80%.

While we have made great strides in increasing awareness among patients of the need for screening, overall screening rates remain well below our national target of 80% and significant disparities in screening persist. By disseminating key information about risk factors, promoting early detection through evidence-based screening, continuing to improve access to care by reducing financial and other barriers, and educating patients about available screening options that best fit their needs and preferences, we can continue to move the needle in improving overall screening rates and optimizing outcomes.

In this month's issue of *GIHN*, we feature an excellent narrative review by Dr. Samir Gupta and colleagues describing the phenomenon of "birth cohort CRC," which is thought to explain recent changes in CRC epidemiology, including rising incidence of early-onset colorectal cancer. We also highlight a timely study out of Kaiser Permanente investigating how best to communicate with patients with prior low-risk adenomas regarding updated colonoscopy intervals given recent guideline changes extending surveillance intervals from 5 to 7-10 years. This question is particularly relevant to resource-constrained healthcare settings, where proactive de-implementation of outdated surveillance intervals could improve access for other patients with more immediate need.

In our March Member Spotlight, we feature Dr. Andy Tau of Austin Gastroenterology, who shares important insights regarding his career as a GI hospitalist, a growing area of GI practice. Finally, in this month's Perspectives column, Drs. Michael Weinstein of Capital Digestive Care and Paul Berggreen of GI Alliance provide powerful contrasting perspectives highlighting the pros and cons of private equity in GI and how to evaluate if it's right for your practice. I found it to be a particularly fascinating read!

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



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GI&Hepatology News

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Frontline Medical Communications Society Partners
Editor Richard Pizzi
Creative Director Louise A. Koenig
Director, Production/ Manufacturing Rebecca Slebodnik
Director, Business Development Cheryl Wall
978-356-0032 cwall@mdedge.com
E-mail ginews@gastro.org

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Member SPOTLIGHT

The Gamer Who Became a GI Hospitalist and Dedicated Endoscopist

BY JENNIFER LUBELL
MDedge News

Reflecting on his career in gastroenterology, Andy Tau, MD (@DrBloodandGuts on X), claims the discipline chose him, in many ways.

"I love gaming, which my mom said would never pay off. Then one day she nearly died from a peptic ulcer, and endoscopy saved her," said Dr. Tau, a GI hospitalist who practices with Austin Gastroenterology in Austin, Texas. One of his specialties is endoscopic hemostasis.

Endoscopy functions similarly to a game because the interface between the operator and the patient is a controller and a video screen, he explained. "Movements in my hands translate directly onto the screen. Obviously, endoscopy is serious business, but the tactile feel was very familiar and satisfying to me."

Advocating for GI hospitalists and the versatile role they play in hospital medicine is another passion of his. "The dedicated GI hospitalist indirectly improves the efficiency of an outpatient practice, while directly improving inpatient outcomes, collegiality, and even one's own skills as an endoscopist," Dr. Tau wrote


Austin Gastroenterology

Dr. Tau

in an opinion piece in *GI & Hepatology News* (2022 Jan 1. www.mdedge.com/gihepnews/article/250039/practice-management/are-gi-hospitalists-future-inpatient-care).

He expounded more on this topic and others in an interview, recalling what he learned from one mentor about maintaining a sense of humor at the bedside.

Q: You've said that GI hospitalists are the future of patient care. Can you explain why you feel this way?

Dr. Tau: From a quality perspective, even though it's hard to put into one word, the care of acute GI pathology and endoscopy can be seen as a specialty in and of itself. These skills include hemostasis, enteral access, percutaneous endoscopic gastrostomy (PEG), balloon-assisted enteroscopy, luminal stenting, advanced tissue closure, and endoscopic retrograde cholangiopancreatography. The greater availability of a GI hospitalist, as opposed to an outpatient GI doctor rounding at the ends of days, likely shortens admissions and improves the logistics of scheduling inpatient cases.

From a financial perspective, the landscape of GI practice is changing because of GI physician shortages relative to increased demand for outpatient procedures. Namely, the outpatient gastroenterologists simply have too much on their plate and inefficiencies abound when they have to juggle inpatient and outpatient work. Thus, two tracks are forming, especially in large busy hospitals. This is the same evolution of the pure outpatient internist and inpatient internist 20 years ago.

Q: What attributes does a GI hospitalist bring to the table?

Dr. Tau: A GI hospitalist is one who can multitask through interruptions, manage end-of-life issues, craves therapeutic endoscopy (even if that's hemostasis), and can keep more erratic hours based on the number of consults that come in. She/he tends to want immediate gratification and doesn't mind the lack of continuity of care. Lastly, the GI hospitalist has to be brave and yet careful as the patients are sicker and thus complications may be higher and certainly less well tolerated.

Q: Are there enough of them going into practice right now?

Dr. Tau: Not really! The demand seems to outstrip supply based on what I see. There is a definite financial lure as the market rate for them rises (because more GIs are leaving the hospital for pure outpatient practice), but burnout can be an issue. Interestingly, fellows are typically highly trained and familiar with inpatient work, but once in practice, most choose the outpatient track. I think it's a combination of work-life balance, inefficiency of inpatient endoscopy, and perhaps the strain of daily, erratic consultation.

Q: You received the 2021 Travis County Medical Society (TCMS) Young Physician of the Year Award. What achievements led to this honor?

Dr. Tau: I am not sure I am deserving of that award, but I think it was related to personal risk and some long hours as a GI hospitalist during the COVID pandemic. I may have the unfortunate distinction of performing more procedures on COVID patients than any other physician in the city. My hospital was the largest COVID-designated site in the city. There were countless PEG tubes in COVID survivors and a lot of bleeders for some reason. A critical care physician on the front lines and health director of the city of Austin received Physician of the Year, deservedly.

Q: What teacher or mentor had the greatest impact on you?

Dr. Tau: David Y. Graham, MD, MACG, got me into GI as a medical student and taught me to never tolerate any loose ends when it came to patient care as a resident. He trained me at every level — from medical school, residency, and through my fellowship. His advice is often delivered sly and dry, but his humor-laden truths continue to ring true throughout my life. One story: My whole family tested positive for *Helicobacter pylori* after my mother survived peptic ulcer hemorrhage. I was the only one who tested negative! I asked Dr Graham about it and he quipped, "You're lucky! It's because your mother didn't love (and kiss) you as much!"

Even to this moment I laugh about that. I share that with my patients when they ask about how they contracted *H. pylori*. ■

LIGHTNING ROUND

Favorite junk food?
McDonalds fries

Favorite movie genre?
Psychological thriller

Cat person or dog person?
Dog

Favorite Halloween costume?
Ninja turtle

Favorite sport?
Football (played in college)

Introvert or extrovert?
Extrovert unless sleep deprived

Favorite holiday?
Thanksgiving

Book you read over and over:
Swiss Family Robinson

Favorite travel destination?
Hawaii

Optimist or pessimist?
Happy pessimist

FDA OKs First Oral Agent for Eosinophilic Esophagitis

BY MEGAN BROOKS

The US Food and Drug Administration (FDA) has approved budesonide oral suspension (Eohilia, Takeda), the first oral treatment for eosinophilic esophagitis (EoE).

Budesonide oral suspension is a corticosteroid indicated for 12 weeks of treatment of EoE in adults and children as young as 11 years.

It will be available in 2-mg/10-mL single-dose stick packs.

"With Eohilia, it's gratifying to now have an FDA-approved treatment specifically formulated for a consistent dose delivery with demonstrated ability to address esophageal inflammation and EoE dysphagia symptoms," said Ikuo Hirano, MD, director of the Esophageal Center at Northwestern University Feinberg School of Medicine, Chicago, Illinois.

"With Eohilia, it's gratifying to now have an FDA-approved treatment specifically formulated for a consistent dose delivery with demonstrated ability to address esophageal inflammation and EoE dysphagia symptoms."

The FDA approved budesonide oral suspension for EoE based on efficacy and safety data from two multicenter, randomized, double-blind, parallel-group, placebo-controlled 12-week studies.

In study 1, significantly more patients receiving active treatment achieved histologic remission (53.1% vs 1% with placebo). The same was true in study 2, with 38% of patients receiving active treatment achieving histologic remission compared with 2.4% of those receiving placebo.

The absolute change from baseline in the patient-reported Dysphagia Symptom Questionnaire combined score was -10.2 with budesonide vs -6.5 with placebo in study 1 and -14.5 vs -5.9 in study 2.

During the last 2 weeks of treatment, more patients receiving budesonide oral suspension experienced no dysphagia or experienced only dysphagia that "got better or cleared up on its own" compared with those receiving placebo, the company said.

The most common adverse reactions seen in the clinical trials of budesonide oral suspension for EoE included respiratory tract infection (13%), gastrointestinal mucosal candidiasis (8%), headache (5%), gastroenteritis (3%), throat irritation (3%), adrenal suppression (2%), and erosive esophagitis (2%). ■

Ultrasound Monitoring of IBD May Prompt Faster Treatment Change

BY KERRY DOOLEY YOUNG

Monitoring inflammatory bowel disease (IBD) with intestinal ultrasound (IUS) appeared to lead to earlier treatment changes and faster remission for patients, compared with conventional disease monitoring, according to a small retrospective analysis.

"Current disease monitoring tools have significant limitations," said Noa Krugliak Cleveland, MD, director of the intestinal ultrasound program at the University of Chicago in Illinois. "Intestinal ultrasound is an innovative technology that enables point-of-care assessment."


Dr. Cleveland

Dr. Cleveland presented the findings at the October 2023 American College of Gastroenterology's annual scientific meeting in Vancouver, British Columbia, Canada.

The analysis was based on 30 patients with IBD in an ongoing real-world prospective study of upadacitinib (Rinvoq, AbbVie) who were not in clinical remission at week 8. For 11 patients, routine clinical care included IUS; the other 19 patients were monitored using a conventional approach.

In the study, both groups were almost evenly split in terms of diagnosis. In the IUS group, four patients had Crohn's disease and five had ulcerative colitis. In the conventional management group, six had Crohn's disease and five had ulcerative colitis.

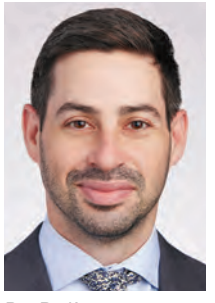
The primary endpoint was time to treatment change.

For the secondary endpoint, the researchers defined clinical remission as a Simple Clinical Colitis Activity Index ≤ 2, or Harvey-Bradshaw Index ≤ 4, and by IUS as bowel wall thickness ≤ 3 mm in the colon or terminal ileum and no hyperemia by color Doppler signal.

The average time to treatment change in the IUS group was 1.1 days, compared with 16.6 days for the conventional management group, Dr. Cleveland reported.

The average time to clinical remission was 26.8 days for the IUS group, compared with 55.3 days for the conventional management group.

The delays in treatment change in the conventional management group were attributed to awaiting test results and endoscopy procedures, as well as communications among clinical team members.


Dr. Dolinger

Strengths of this research project included its prospective data collection and the experienced sonographers who participated, Dr. Cleveland and colleagues said. Limitations included retrospective analysis, a small number of patients on a single therapy, and the potential for bias in patient selection.

Studies of other therapies and a prospective trial are underway.

During the presentation, Dr. Cleveland commented about what kinds of treatment changes were made for patients in the study. They commonly involved extending the induction time, and, in some cases, patients were switched to another treatment, she said.

In an interview, Michael Dolinger, MD, of the Icahn School of Medicine at Mount Sinai in New York, said more research needs to be done to show whether IUS will improve outcomes.

"They're showing that they make more changes sooner," he said. "Does that actually affect and improve outcomes? That's the big question."

Dr. Dolinger said the concept for using IUS is that it helps physicians catch disease flares earlier and respond faster with changes to the treatment plan, thus preventing the buildup of chronic bowel damage.

"That's the concept, but that concept is actually not so proven in reality" yet, he said. "But I do believe that they're on the right path."

In Dr. Dolinger's view, adding ultrasound provides a more patient-centric approach to care of people with IBD. With more traditional approaches, patients often are waiting for results of tests done outside of the visit, such as MRI.

The concept for using intestinal ultrasound is that it helps physicians catch disease flares earlier and respond faster with changes to the treatment plan, thus preventing the buildup of chronic bowel damage.

"With ultrasound, I am walking them through the results as it's happening in real time during the clinic visit," Dr. Dolinger said. "I am showing them on the screen, allowing them to ask questions. They're telling me about their symptoms, as I'm putting the probe on where it may hurt, as I'm showing them inflammation or healing. And that changes the whole conversation."

The study received support from the Mutchnik Family Foundation. Dr. Cleveland reported financial relationships with Bristol Myers Squibb, Neurologica, and Takeda. Her coauthors reported financial relationships with multiple drug and device makers.

Dr. Dolinger said he is a consultant for Samsung's Neurologica, which makes ultrasound equipment. ■

Automated ADR Software Shows Promise

BY WILL PASS
MDedge News

FROM TECHNIQUES AND INNOVATIONS IN GASTROINTESTINAL ENDOSCOPY

Automated software for calculating adenoma detection rate (ADR) and other colonoscopy performance metrics could expedite the quality review process and open doors to new benchmarks, according to investigators.

The new software, which automatically integrates endoscopy and pathology reports across a variety of practice settings, delivered an ADR on par with manual review, supporting its accuracy and feasibility for real-world usage, reported Todd A. Brenner, MD, of Johns Hopkins Hospital, Baltimore, Maryland, and colleagues.

"ADR calculation is resource-intensive, often requiring manual collation of endoscopy and pathology data across multiple reporting modalities, making it an impractical tool for frequent quality audits at many centers," the investigators wrote in *Techniques and Innovations in Gastrointestinal Endoscopy* (2023 Jul 28. doi: 10.1016/j.tige.2023.07.004).

Although others have tried to streamline ADR calculation, most efforts have relied upon manual entry of pathology data, while approaches using artificial intelligence tend to be costly and clumsy to implement across different databases, according to the investigators.

"Thus, there is a substantial demand for a novel tool to extract and analyze colonoscopy indicators from text-based reports that provides accurate data extraction in a package that is easily implemented and modified by clinicians," they wrote.

Dr. Brenner and colleagues developed a web-based platform to meet these goals.

Following colonoscopy, the system gathers procedural and histopathology results, extracts and classifies relevant data, then outputs ADR, along with cecal intubation rate, Boston Bowel Preparation Score (BBPS), and withdrawal time.

The software was evaluated using endoscopy and pathology reports from 3809 colonoscopies performed at six centers over 3 months. Six months later, the investigators manually reviewed data from a validation cohort of 1384 colonoscopies conducted over a 1-month period.

Comparing the automated and manual approaches revealed high congruity, with an ADR of 45.1% for the automated system vs 44.3% for manual review. The software also correctly identified most ADR-qualifying screening colonoscopies (sensitivity, 0.918; specificity, 1.0).

"The discrepancy between manual and automated ADR calculations was exclusively attributable to missed (i.e., false negative) identification of ADR-qualifying procedures," the investigators wrote.

Of these 43 mislabeled cases, about half involved pending pathology results or erroneous pathology sample entries, while the remainder were due to spelling and/or syntax issues that stumped the system.

Still, Dr. Brenner and colleagues suggested that additional programming can overcome these kinds of issues and allow for generalizability across institutions. They noted that search terms can be edited to match local practice patterns, while the web-based reporting platform can be customized to deliver desired quality metrics.

The publication includes a screenshot of one such dashboard, including a readout of ADR, a comparison of ADR across sexes, a pie chart of BBPS score distribution, and gauge charts for cecal intubation rate and mean withdrawal time.

"Further development of this Internet-based colonoscopy quality reporting platform will focus on integrating additional metrics, such as adenomas per colonoscopy, as well as novel metrics, such as a size-stratified ADR, location-stratified ADR, or ADR stratified by polyp histology," the investigators wrote.

They predicted that automating data collection in this way could help determine which metrics provide clinically meaningful insights, potentially expanding the roster of standard performance benchmarks.

"We further intend to study the integration of this platform into colonoscopy quality improvement and transparency programs to better characterize the impact of frequent, on-demand ADR feedback on colonoscopy performance," Dr. Brenner and colleagues concluded.

The investigators disclosed relationships with Olympus, Medtronic, Apollo Endosurgery, and others. ■

Adenoma detection rate (ADR) has proven to be a useful metric for the evaluation of quality in screening colonoscopies. Outside of its proven inverse associations with interval colon cancer, ADR also can facilitate quality improvement interventions aimed at improving colonoscopy quality among low performing endoscopists. By focusing on this metric, healthcare providers can identify areas for improvement, ensuring a higher standard of care and ensuring maximum benefit of screening colonoscopies for patients.


Dr. Rao

However, the metric is only of value if it can evolve outside of the research setting and into clinical practice. The substantial burden of combining endoscopic and pathology reports, which are often contained in two separate reporting systems, has led to the limited reporting of this metric.

Brenner and colleagues describe an automated system importing smart-phrase–based pathology reports into the endoscopy reporting software allowing for the subsequent calculation of an endoscopist-specific ADR. The automated reporting system provided a high level of agreement against manual review and correlated with average withdrawal time. Additional available quality metrics included cecal intubation rate and individual endoscopist procedural volumes.

The added methodology for developing endoscopist and site-specific ADR is an exciting and potentially more generalizable tool that will allow for widespread adoption of this quality metric. Site-specific data limitations and the use of smart-phrase–based reporting systems may limit the utility of this methodology, but it can also encourage more uniform reporting in pathologic and endoscopic reports. Regular service intervals may be required to inspect the quality of the reporting when initially implementing systems at a variety of practice settings.

Vijaya L. Rao, MD, is assistant professor of medicine in the Division of Digestive Diseases & Nutrition at Rush University Medical Center, Chicago, Illinois. She reports no conflicts of interest.

AGA Updates Polypectomy Guidance

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

The American Gastroenterological Association (AGA) has published a clinical practice update on polypectomy techniques.

The new guidance document, authored by Andrew P. Copland, MD, of the University of Virginia Health System, Charlottesville, and colleagues, includes 12 pieces of best practice advice pertaining to polyp removal, including the need for evaluation, considerations for selecting a resection strategy, and reasons for referral.

"Polypectomy techniques are continually evolving with improvements in the ability to assess polyps for high-risk features and with development of appropriate procedures for complete and safe polyp resection," the authors wrote in *Clinical Gastroenterology and Hepatology* (2023 Nov 28. doi: 10.1016/j.cgh.2023.10.012). "This clinical practice update provides guidance in characterizing polyps and choosing appropriate polypectomy techniques for polyps 2 cm or less in size, which comprise most polyps encountered by most endoscopists."

To begin, they advised a "structured visual assessment using high-definition white light and/or electronic chromoendoscopy and with

Continued on page 8

Alisha Mavis, MD
Pediatric Hepatologist; Levine Children's Hospital, Atrium Health, Charlotte, NC

Developed under the direction and sponsorship of Ipsen Biopharmaceuticals.

Faculty Disclosure: Dr. Mavis discloses that she has been paid consulting fees by Ipsen.

NON-US-003685 January 2024

Alagille Syndrome

Alagille syndrome (ALGS) is a multiorgan, systemic syndrome characterized by impaired bile duct function leading to chronic cholestasis, as well as cardiac and vascular abnormalities, vertebral abnormalities, and ocular changes.[1,2] Patients may have all or some combination of these characteristic defects. ALGS is an inherited, autosomal dominant syndrome caused by mutations in genes that regulate the NOTCH signaling pathway; approximately 90% of ALGS is related to pathogenic variants in *JAG1*, with most of the remainder having variants in *NOTCH2*.[2,3] Additional variants and mutations are being identified with genome and next-generation sequencing, and as yet unidentified variants may be present in patients who are clinically diagnosed but genetically negative.[4,5] The variants result in aberrant and inadequate hepatic bile duct development (bile duct paucity); however, NOTCH signaling is also integral to healthy structural development of the heart, kidneys, spine, facial bone structure, and blood vessels.[1]

ALGS is a rare syndrome with an estimated incidence of 1/30,000-50,000 live births; genetic testing will likely refine this estimate.[1] The long-term risks associated with ALGS include progressive liver injury and need for liver transplant, cardiovascular disease, impaired growth, ocular disturbances, vascular complications, and decreased renal function. ALGS is highly variable, ranging from no apparent clinical involvement to severe disease that requires liver transplant.[1] Several natural history studies have shown that elevated bilirubin (≥5.0 mg/dL) in infancy (age 6-12 months) is associated with higher risk for hepatic complications.[1,2,6]

Diagnosis and Challenges

Diagnosis is challenged by the variety of symptoms and heterogeneous phenotypes of ALGS, with some patients having silent disease and others exhibiting severe symptoms at diagnosis.[7] In one review of available data, age at ALGS presentation varied from less than 4 months to 10 years, with most children being diagnosed before 12 months of age.[1] In ALGS, infants typically present with evidence of cholestasis within 3 months of birth. Over time, symptoms of persistent jaundice, poor early childhood growth, xanthomas, and—especially—intense pruritus develop. Cholestasis in infants or children often triggers a workup for ALGS. I find that children without liver symptoms typically are not diagnosed until they are older.

The diagnostic criteria for ALGS includes structural or physical changes in multiple organ systems and laboratory testing suggestive of the disease; genetic testing is not required to make a diagnosis. Hepatic, cardiac, ocular, craniofacial, and skeletal abnormalities are highly prevalent with ALGS, with at least one found in ≥87% of patients; up to 100% of patients have bile duct paucity.[7-9] Recently revised criteria for clinical diagnosis of ALGS require ≥4 of these abnormalities in the absence of genetic confirmation **(Table 1)**.[7] Genetic testing with a multigene panel that includes *JAG1* and *NOTCH2* can be used.[3] In my experience, clinical diagnosis often can be made and medical treatment initiated while waiting for results of laboratory or genetic testing—which may take weeks. With genetic testing, biopsy is no longer a necessity.[3] Liver and kidney function tests, lipid levels (generally elevated in ALGS), and levels of fat-soluble vitamins (generally lower in ALGS) are part of the workup. Imaging tests include spine radiograph, echocardiogram, and abdominal ultrasound.[9] The differential diagnosis includes infectious as well as other hepatobiliary diseases, such as α1-antitrypsin deficiency and biliary atresia.

Intense pruritus associated with ALGS is related to cholestasis and differs from immune-mediated pruritus seen in childhood, such as eczema and atopic dermatitis. It is almost universally present through childhood and into adulthood **(Figure 1)**.[1,2] To improve diagnosis, pediatricians should know to recognize symptoms—such as jaundice, xanthomas, and poor growth, as well as nonresponse to eczema therapies—that suggest a hepatic source of the itch. Redness and edema, intrinsic to histaminic pruritus, generally are absent in cholestatic pruritus.[10] In

Table 1. Revised Diagnostic Criteria for Diagnosis of ALGS

NOTE:
- ≥4 major criteria are required for the diagnosis of ALGS
- With family history of ALGS, presence of *JAG1* mutation is diagnostic, even if none of these criteria are present
- If either genetic mutation or family history is positive, at least 1 major criterion is needed to make the diagnosis

Major Criteria: Organ System (% of Involvement)	**Most Common Findings**
Hepatic (75-100%)	Bile duct paucity, cholestasis
Cardiac/vascular (85-98%)	Peripheral pulmonary artery stenosis; intracranial or intra-abdominal aneurysm
Skeletal (33-87%)	"Butterfly" vertebrae
Renal (19-73%)	Anomalies in renal tubules
Ocular (56-88%)	Posterior embryotoxon—grayish circle in posterior cornea
Facial structure (70-98%)	Broad forehead, deep-set eyes, pointed chin

Adapted from Menon (2022).[7]

the GALA natural history study, 95% had neonatal cholestasis and 74% developed pruritis (n = 761/1028), with a median age at onset at 12 months. Xanthomas developed in 24% (n=243/980), with median age at onset of 25 months.[6]

Management of ALGS

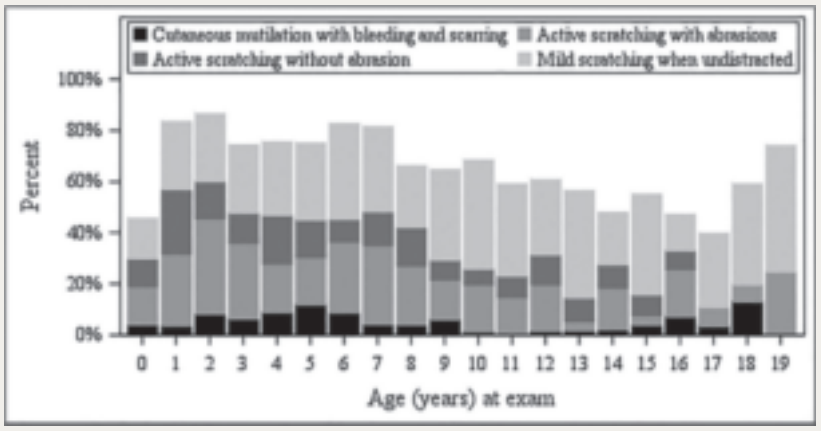
Because of its many manifestations, ideal management of ALGS requires a multidisciplinary approach with coordination between hepatology, cardiology, and renal specialists and open communication with pediatricians and the child's other healthcare providers. Although the pediatrician seems to be centrally located for coordinating, in my experience, hepatology is the medical home for these families. My practice coordinates follow-up for appointments, school performance, additional testing, and symptom management. Some patients stay with us throughout their college years.

Over the long term, the impact of ALGS on liver health is a deep concern, but in the daily life of patients and families, managing cholestatic pruritus has the most immediate impact in terms of improving quality of life. In my practice, pruritus usually has the greatest impact on daily life, appears to be the most debilitating, and is the one symptom that almost all families and patients complain about. My philosophy when speaking with families is to focus first and foremost on current symptoms and to manage those—pruritus, then perhaps growth and nutrition, then long-term liver health as needed. Of available medical therapies for ALGS, choleretic agents are typically the first choice to manage cholestasis and can decrease bile-related hepatotoxicity.[11]

Unresolved pruritus is the most bothersome and often most difficult symptom to manage. It undermines sleep for both the child and the family and, when the child reaches older ages, can affect educational and social development. Pruritus often improves when biochemical markers of cholestasis improve, offering one pathway to treatment.[2] Class of therapies approved to treat ALGS/cholestatic pruritus are summarized in **Table 2**.[7,11]

Fat metabolism and absorption of fat-soluble vitamins are altered in ALGS. These should be addressed and can contribute to malnutrition. Diets should be high in carbohydrates (40%-60%) and fats (30%-50%), with medium-chain triglycerides making up 30% of fats. Vitamins A, D, E, and K should be augmented to achieve healthy levels.[7] Patients should have regular follow-up with pediatric cardiology, neurology, nephrology, and ophthalmology. Children will need to be followed into adulthood and transitioned to adult care, an area of intense research that is still evolving.

Figure 1. Prevalence and Severity of Pruritus Among Patients With ALGS Over Time



Adapted from Kamath (2020).[2]

Table 2. Medical Treatment of Cholestatic Pruritus in ALGS

Class	Mechanism of Action
Choleretic agent	Protects liver and bile ducts; typical first-line medical therapy in ALGS; limited effect on pruritus
Bile acid sequestrant	• Approved for cholestatic pruritus in adults • Minimally effective in ALGS, where lack of bile acids is characteristic; may impede fat-soluble vitamin absorption
Antimicrobial	Induces 6 alpha-hydroxylation of bile cells; mechanism in cholestatic pruritus unclear; side effects include nausea, hepatitis risk
Opioid antagonist	Not approved for pediatric use
Selective serotonin-reuptake inhibitor	Minimal data in ALGS suggest it is effective, but side effects may be limiting
Ileal bile acid transport inhibitors	• Approved for cholestatic pruritus in patients ≥3 months • Approved for cholestatic pruritus in patients ≥12 months
Antihistamine	Limited efficacy due to different pruritus triggers in ALGS than other childhood pruritus

Adapted from Menon (2022),[7] and Rodrigo(2023)[11]

Families and ALGS

A family-centered approach is crucial to successful management, as all family members are affected and may participate in the patient's care. In my experience, families need large-scale education about the syndrome and management, and the pediatric hepatology team provides most of it. The pediatric hepatology team also provides support and direction on where to find information. In general, I find that resources for families are lacking. One excellent resource is the Alagille Syndrome Alliance, where families can share experiences as well as learn about the syndrome and its management.

Parents may wonder about their other current or future children and ALGS risk. Genetic tests may be used to screen family members of patients for existing disease or risk for future children, with genetic counseling to provide context.[3]

Awareness of ALGS can facilitate timely diagnosis, with the caveat that different children present with different symptoms that require individualized, stepwise approaches. Unfortunately, with current knowledge we cannot predict the disease course for any individual child. We only know that over time some percentage will require a transplant, but there is no way to predict when or whether that will occur. I try to keep families in the present and assure them that we will deal with symptoms as they arise. It is important to urge them to live in the here and now with their children. My approach is to emphasize to each family that their job is to love and care for their child as they would any other child, as a healthy child, and to allow their child to participate in life and not have their syndrome define them.

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Gastric Cancer Screening Benefits Vary by Country

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

South Korea's gastric cancer (GC) screening program has reduced disease-related mortality by 41%.

Japan's? Not at all.


Mr. Sun

These findings suggest that the benefits of nationwide gastric cancer screening may vary widely between countries while offering insights into program best practices, reported lead author Dianqin Sun, a PhD candidate at the University Medical Center, Rotterdam, the Netherlands, and colleagues.

"Despite the lack of evidence from randomized controlled trials, South Korea and Japan, two countries with a high GC incidence, have been at the forefront of GC secondary prevention and have implemented nationwide organized GC screening programs for decades using endoscopy or upper gastrointestinal series," the investigators wrote in *Gastroenterology* (2023 Nov 24. doi: 10.1053/j.gastro.2023.11.286).

Although individual-level data from both programs supports their efficacy in reducing GC-related death, the investigators noted that these studies have been limited by volunteer bias, and population-level data remain scarce.

To address this knowledge gap, Mr. Sun and colleagues used the flexible synthetic control method to determine how screening programs affected GC mortality rate, as well as a composite mortality rate for esophageal cancer and peptic ulcer.

"The concept of the synthetic control method is to construct a synthetic control for the treated country by deriving a weighted average of multiple control countries without intervention," the investigators wrote. "The weight of controls is determined in a data-driven way to minimize the differences in preintervention outcomes (i.e., GC mortality before the introduction of nationwide screening) and other covariates associated with GC mortality between the treated country and the synthetic control."

This approach revealed starkly different benefits for South Korea and Japan.

Compared with the synthetic control, South Korea's screening program was associated with a 17% reduction in GC mortality risk on average, with risk dropping as far as 41% after the 15th year of screening.

The Korean program was also associated with a 28% reduction in mortality from esophageal cancer and peptic ulcer, with this rate decreasing as much as 53% after 15 years of screening.

In sharp contrast, Japan's mortality rates for GC and the other GI diseases were not significantly different from the synthetic control after 34 years of screening.

The investigators suggested several possible factors behind the

Continued on following page

Gastric cancer (GC) is the fourth leading cause of cancer-related death worldwide. It remains a common cancer in some Asian countries and among Asian immigrants in western countries.


Dr. Chan

To date, only Japan and South Korea have national GC screening programs. Previous observational data from these screening programs indicated their effectiveness in reducing GC mortality but were susceptible to volunteer bias. The population impact of these national programs remains uncertain.

Sun et al. used a quasi-experimental design to estimate the effect of these two countries' screening programs on age-standardized GC mortality and other upper gastrointestinal (UGI) diseases (esophageal cancer and peptic ulcer) among people aged above 40 years. The investigators found that the national program in South Korea was associated with a 41% reduction in GC mortality and a 53% reduction in the mortality of other UGI disease mortality by the 15th year after the start of the program. However, the effect on gastric cancer mortality in Japan was uncertain. The effects were robust for South Korea across different analyses whereas the results for Japan were susceptible to bias.

The disparities in screening programs between South Korea and Japan suggest that factors like screening method, participation rates, and organizational strategies might influence the effectiveness of GC screening. Currently, at least two large-scale randomized trials of GC screening are underway. It remains uncertain how the experience from South Korea and Japan will inform GC screening policy in other countries.

Francis K.L. Chan, MD, is professor of medicine at The Chinese University of Hong Kong. He has no conflicts to declare in relation to this commentary.

Continued from page 5

photodocumentation" for all polyps identified during routine colonoscopy, with close attention to any features suggesting submucosal invasion.

Next, in a series of statements, the guidance document steers appropriate use of various cold and hot polypectomy techniques.

Cold snare polypectomy should be used for polyps less than 10 mm in size, while cold forceps may be considered for polyps 1-3 mm in diameter. Cold resection techniques should also be used for serrated polyps, with use of submucosal injection, if needed, for polyps greater than 10 mm with unclear margins.

For polyps of intermediate size (10-19 mm), both cold and hot snare polypectomy should be considered, alongside endoscopic mucosal resection for polyps, Dr. Copland and colleagues wrote, noting that hot snare polypectomy should be used for removal of pedunculated lesions greater than 10 mm in size.

In contrast, the update advises against use of hot forceps polypectomy in any scenario.

"Hot forceps polypectomy for diminutive and small polyps is associated with higher incomplete polyp removal rates compared with cold snare polypectomy," the update panelists wrote. "It is also associated with higher risks of postpolypectomy hemorrhage, particularly in the right colon with higher risks of deep thermal injury.

"Polypectomy techniques are continually evolving with improvements in the ability to assess polyps for high-risk features and with development of appropriate procedures for complete and safe polyp resection."

Therefore, the use of hot forceps polypectomy is discouraged."

In another best practice advice statement, the panelists advised against routine use of clips to close resection sites for polyps less than 20 mm. For larger polyps, they advised "selective use" of clips, most suitably in the proximal colon.

Alternatively, patients with polyps at least 20 mm in size should be considered for referral to endoscopic specialty centers, along with patients who have polyps in "challenging" locations, and those with a recurrent polyp at a prior polypectomy site.

Patients with nonpedunculated polyps that exhibit "clear evidence of submucosally invasive cancer" should be referred for surgical evaluation, they added. On a similar note, the update advises tattooing lesions that may need to be located at a future surgery or endoscopy.

Finally, Dr. Copland and colleagues advised all endoscopists to understand appropriate selection of electrosurgical generator settings for various polypectomy or postpolypectomy thermal techniques.

"Ongoing research will allow further tailoring of polypectomy techniques to improve patient outcomes," they concluded.

This clinical practice update was commissioned and approved by the AGA Institute. The working group disclosed relationships with Olympus, Boston Scientific, GIE Medical, and others. ■

Meta-analysis Highlights Litany of Complications From MASLD Across Several Domains

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Metabolic dysfunction–associated steatotic liver disease (MASLD) is linked to a host of negative clinical outcomes across cardiovascular, metabolic, and oncologic domains, based on a large-scale meta-analysis of longitudinal data.

These findings emphasize the multisystemic nature of MASLD, suggesting that broader treatment targets are needed to reduce systemic events and end organ complications, reported lead author Kai En Chan, MBBS, of the National University of Singapore, and colleagues.

"[D]espite the substantial impact of MASLD, with direct medical costs estimated to reach $103 billion in the United States alone, a comprehensive umbrella meta-analysis of the longitudinal complications associated with MASLD has yet to be conducted," the investigators wrote in *Clinical Gastroenterology and Hepatology* (2023 Sep 28. doi: 10.1016/j.cgh.2023.09.018), noting that key outcomes to sex and disease severity have yet to be elucidated. "A comprehensive understanding of the spectrum of clinical complications associated with MASLD is thus crucial in developing effective disease management strategies and optimizing the allocation of limited healthcare resources."

To this end, the investigators analyzed data from 129 studies reporting longitudinal risks of clinical outcomes among adults with MASLD. Assessed complications spanned a broad array of organ systems and pathologies.

Cardiovascular and oncologic conditions predominated, while chronic kidney disease, liver-related outcomes, gallstone formation, dementia, and reflux esophagitis were also considered.

The analysis revealed significant associations between MASLD and — in ascending level of risk — chronic kidney disease (hazard ratio [HR], 1.38), cardiovascular diseases (HR, 1.43), cancer (HR, 1.54), prediabetes (HR, 1.69), hypertension (HR, 1.75), diabetes (HR, 2.56), and metabolic syndrome (HR, 2.57).

Across cardiovascular diseases, MASLD raised risk of hypertension the most, by 75%. Among cancer types, MASLD increased risk of hepatocellular carcinoma to the greatest degree, by more than fourfold.

No significant sex-specific differences in MASLD-linked risk were detected for cancer, chronic kidney disease, diabetes, or cardiovascular disease, although the investigators urged a cautious interpretation of these findings, since relevant data were scarce.

"It is imperative to understand that MASLD is a complex and multifaceted condition that requires a comprehensive approach to recognition and treatment beyond that of the hepatologist alone," the investigators wrote.

They also suggested that the link between MASLD and cancer deserves particular attention.

"Although the mechanism by which MASLD gives rise to cardiovascular disease and diabetes has been thoroughly researched, the pathophysiology of MASLD leading to extrahepatic carcinogenesis is less well understood and has been postulated to be linked to chronic inflammation and dysregulation of the gut microbiome in MASLD," they wrote.

Lastly, considering the multiprong association between MASLD and so many complications, the investigators recommended broader clinical metrics for measuring outcomes in patients with MASLD.

"With the synergistic increases of metabolic diseases globally, treatment targets should in turn act beyond the resolution of fibrosis but also to reduce systemic end organ complications," they concluded.

The investigators disclosed relationships with AbbVie, Echosens, Gilead Sciences, and others. ■

In a massive meta-analysis of 129 studies that included over 6 million participants, Chan and colleagues evaluated the associations of MASLD with incident hepatic and extrahepatic outcomes. They report numerous associations for MASLD with metabolic, cardiovascular, and renal events as well as with gastrointestinal, hepatobiliary, and other types of cancers.


Dr. Gawrieh

Some of their findings are congruent with prior research establishing the independent relationship of MASLD with future development of cardiovascular and renal disease, diabetes, and hepatocellular carcinoma. It is, however, unclear if the additional MASLD linkages they report, such as with nonliver malignancies, would persist if adjustment for relevant covariates affecting these outcomes were performed. While the large number of participants from different study populations included in the analysis can be a strength, the resulting considerable heterogeneity calls for caution in interpreting some of the associations and their magnitudes.

The unimpeded pace of the obesity pandemic remains a steady driver of the rise in the burden of metabolic syndrome and its components, including MASLD. Thus, approaches to tackle the rising burden of metabolic diseases including MASLD should start with the root driver, obesity. It is also imperative to consider addressing the cardiometabolic milieu in any approach designed to specifically target MASLD/MASH. Lifestyle modifications that include weight loss, smoking cessation, and avoidance of alcohol use may help reduce risks of cardiovascular disease and cancer, the leading causes of death in patients with MASLD. Anticipated pharmacologic therapies for MASH should not only improve liver endpoints but also have a beneficial or, at minimum, neutral extrahepatic effects on coexisting cardiometabolic conditions.

Samer Gawrieh, MD, is professor of clinical medicine in the Division of Gastroenterology and Hepatology at Indiana University School of Medicine, Indianapolis, where he serves as the Director of Hepatology Research and Clinical Fellowship Program. He receives funding for the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute on Alcohol Abuse and Alcoholism, and research grant support from Zydus and Viking, and serves on safety committees with TransMedics, Pfizer, and Spruce.

Continued from previous page

lack of benefit in Japan, including the absence of a recommendation for endoscopic screening until 2014. In 2015, just 19% of municipalities in Japan were using endoscopy for screening, compared with more than 72% in South Korea in 2011. Furthermore, guideline adherence and screening program adherence are lower in Japan than in South Korea, they noted.

"Therefore, the findings in our study may have been expected," the investigators wrote. "However, it is important to note that certain covariates were unavailable for the analysis in Japan, which may have introduced potential biases, the directions of which are unclear. Further studies are needed to compare the screening impact in South Korea and Japan."

Meanwhile, the present results could guide screening programs around the world, Mr. Sun and colleagues suggested.

"This [study] highlights the significance of a well-planned organizational structure and evidence-based decision making when organized screening is started," they wrote. "With a quasi-experimental design, this study will facilitate triangulating current observational evidence and provide valuable insights while the GC screening randomized controlled trials are still underway. The data and experience from South Korea and Japan will inform GC screening policy in other countries."

The investigators disclosed no conflicts of interest. ■

Dueling Gut Bacteria Impact Chronic HBV Progression

BY WILL PASS
MDedge News

FROM CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Two species of gut bacteria modulate the immune system and even the survival of one another to impact the progression of chronic hepatitis B (CHB), according to investigators.

While *Ruminococcus gnavus* promotes immune tolerance and therefore hepatitis B virus (HBV) persistence, *Akkermansia muciniphila* stimulates the immune system, promoting viral clearance, reported lead author Huey-Huey Chua, MD, of the National Taiwan University College of Medicine and Children's Hospital, Taipei, and colleagues.

These findings could lead to new therapeutic strategies, such as administration of the secretory products of *A. muciniphila*, or provision of probiotics and prebiotics that tip the balance toward this more beneficial bacterium, the investigators wrote in *Cellular and Molecular Gastroenterology and Hepatology* (2023 Dec 12. doi: 10.1016/j.jcmgh.2023.12.003).

Their study, which included data from both human patients and mouse models of CHB, was grounded in prior research showing a link between gut microbiota and the age-dependence of HBV immunity.

"Sterilization of the gut microbiota using antibiotics prevents adult mice from rapidly clearing HBV and restores the tolerance phenotype, implying that the gut microbiota may transmit signals to break liver tolerance and evoke rapid HBV clearance," Dr. Chua and colleagues wrote. "We hypothesized that the wax and wane of gut microbiota signatures may determine the progression of CHB. We aimed to delineate what the pivotal bacteria are and how they manipulate the progression of CHB."

They began by analyzing fecal samples from 102 patients with CHB either in the immune-tolerant (IT) or immune-active (IA) phase of infection.

R. gnavus was the most abundant species among IT patients, whereas *A. muciniphila* was most abundant among patients in the IA phase. Higher levels of *A. muciniphila* were also associated with early hepatitis B e-antigen (HBeAG) loss, HBeAG seroconversion, and flares of aminotransferase. A mouse model echoed these findings.

Further experiments with mouse models revealed that *R. gnavus* modulates bile acids to promote HBV persistence and prolongation of the IT course. In opposition, *A. muciniphila* removes cholesterol and secretes metabolites that inhibit growth and function of *R. gnavus*.

"These novel findings will certainly confer a groundbreaking impact on the future therapy of CHB," Dr. Chua and colleagues wrote.

They went on to describe several therapeutic strategies worth further investigation.

"A key step to promote switching from the IT to IA phase is to lessen the richness of *R. gnavus* and bile acid bioconversion from cholesterol," they wrote. The secretory products of *A. muciniphila* that successfully ameliorate the burden of *R. gnavus* outgrowth can be provided as useful means to induce anti-HBV efficacy. Also, the development of targeted probiotics or prebiotics that can modulate the gut microbiota composition to favor the beneficial effects of *A. muciniphila* while inhibiting the detrimental effects of *R. gnavus* may have translational value for CHB."

The study was supported by the Ministry of Science and Technology, Executive Yuan, Taiwan and the Center of Precision Medicine from Featured Areas Research Center Program within the Framework of the Higher Education Sprout Project by the Ministry of Education in Taiwan. The investigators disclosed no conflicts of interest. ■

Clinical observations have long indicated that chronic hepatitis B (CHB) patients with a prolonged immune-tolerant (IT) phase are at a higher risk of liver diseases, while those with an early transition to the immune-active (IA) phase are associated with a better clinical outcome. However, the underlying mechanisms remain unclear.


Dr. Zeng

In the latest issue of *Cellular and Molecular Gastroenterology and Hepatology*, Chua et al. shed new light on the direct involvement of gut microbiota in regulating the progression of CHB. Specifically, using fecal samples from CHB patients and a hepatitis B virus (HBV) mouse model, the research team demonstrates that the gut bacterium *Ruminococcus gnavus* promotes IT and HBV persistence, while *Akkermansia muciniphila* favors the transition from the IT to IA phase and HBV clearance. Furthermore, *R. gnavus* modulates bile acid metabolism to facilitate HBV replication, while *A. muciniphila* removes cholesterol and secretes metabolites that inhibit the growth and function of *R. gnavus*.

This study merits attention as it marks an important advancement in our understanding of how gut microbiota affects the immune response and, in turn, the progression of CHB, offering insights for potential *A. muciniphila*–based therapies. Nonetheless, the research is still in its infancy, and further studies, including longitudinal analysis to determine gut microbiota changes from IT to IA, are required. The prospect of *A. muciniphila* supplementation could be beneficial for CHB patients, warranting clinical trials. Continued research could lead to improved management and prevention of liver diseases in this patient population with CHB.

Qirong Jiang, MD, and Dawu Zeng, MD, are based in the Hepatology Research Institute, the First Affiliated Hospital, Fujian Medical University, Fuzhou, China. They report no conflicts of interest.

AGA Gives Guidance on Management of Subepithelial Lesions

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

American Gastroenterological Association (AGA) has published a clinical practice update on endoscopic full-thickness resection (EFTR) for the management of gastrointestinal subepithelial lesions (SELs).

The new guidance document, authored by Lionel S. D'Souza, MD, of Stony Brook University Hospital, Stony Brook, New York, and colleagues, offers a framework for deciding between various EFTR techniques based on lesion histology, size, and location.

"EFTR has emerged as a novel treatment option for select SELs," the update panelists wrote in *Gastroenterology* (2023 Dec 18. doi: 10.1053/j.gastro.2023.11.016). "In this commentary, we reviewed the different techniques and uses of EFTR for the management of SELs."

They noted that all patients with SELs should first undergo multidisciplinary evaluation in accordance with a separate AGA guidance document on SELs (Clin Gastroenterol Hepatol. 2022 Nov. doi: 10.1016/j.cgh.2022.05.054).

The present update focuses specifically on EFTR, first by distinguishing between exposed and nonexposed techniques. While the former involves resection of the mucosa and all other layers of the wall, the latter relies upon a "close first, then cut" method to prevent perforation, or preservation of an overlying flap of mucosa.

The new guidance calls for a nonexposed technique unless the exposed approach is necessary.

"In our opinion, the exposed EFTR technique should be considered for lesions in which other methods (i.e., endoscopic mucosal resection, endoscopic submucosal dissection, and nonexposed EFTR) cannot reliably and completely excise SELs due to larger size or difficult location of the lesion," the update panelists wrote.

"The exposed EFTR technique may be best suited for gastric lesions and as an alternative to other endoscopic approaches for SELs in the rectum. The exposed technique

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NEJM Study Highlights Resmetirom's Efficacy in NASH With Liver Fibrosis

BY BECKY MCCALL

The oral thyroid hormone receptor beta-selective agonist resmetirom (Madrigal Pharmaceuticals) in both 80-mg and 100-mg doses was superior to placebo at achieving resolution of nonalcoholic steatohepatitis (NASH) and improving liver fibrosis, according to the results of the ongoing phase 3 MAESTRO-NASH trial published in *The New England Journal of Medicine* (2024 Feb 7. doi: 10.1056/NEJMoa2309000).


Dr. Harrison

Although certain findings from this trial were initially presented at the European Association for the Study of the Liver Congress 2023, the publication of the full peer-reviewed paper represents a potentially significant milestone in the management of NASH, a disease for which there is currently no approved pharmacologic treatment.

"Data for the first 1,050 patients from the MAESTRO-NASH trial, together with data from completed resmetirom trials, support the potential for resmetirom to provide benefit to patients with NASH and liver fibrosis," wrote the authors, led by principal investigator Stephen Harrison, MD, chairman of Pinnacle Clinical Research and Summit Clinical Research in San Antonio, Texas.

The trial uses the earlier nomenclature of NASH and nonalcoholic fatty liver disease (NAFLD). An international consensus group has since changed these terms to metabolic dysfunction–associated steatohepatitis (MASH) and metabolic dysfunction–associated steatotic liver disease (MASLD), respectively.

A Closer Look at MAESTRO-NASH

Investigators enrolled 996 participants who were randomly assigned to receive placebo or resmetirom at 80 mg or 100 mg. Patients were followed for 52 weeks, at which point, they were assessed for the dual primary endpoints of NASH resolution (including a reduction in the NAFLD activity score by ≥ 2 points) with no worsening of fibrosis and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

They observed that patients receiving resmetirom had a significant improvement across both doses and both primary endpoints.

NASH resolution with no worsening of fibrosis was achieved in 25.9% and 29.9% of the patients in the 80-mg and 100-mg groups, respectively, vs 9.7% on placebo. Fibrosis improved by at least one stage with no worsening of the NAFLD activity score in 24.2% and 25.9% of patients in the increasing-dose groups, respectively, compared with 14.2% on placebo ($P < .001$ for both doses compared with placebo).

The effects with resmetirom were consistent across key subgroups, regardless of baseline fibrosis stage; baseline NAFLD activity score; or type 2 diabetes status, age, and sex.

"Multiple non-invasive tests for NASH, steatosis, and fibrosis (including blood biomarkers and imaging) showed a similar direction of effects favoring resmetirom treatment, which supports the findings for the primary end points," Dr. Harrison and colleagues wrote.

The majority of patients with NASH also have diabetes. As a result, patients with NASH are known to have a high cardiovascular risk and mortality. However, MAESTRO-NASH investigators reported that, compared with those receiving placebo, patients on resmetirom experienced reductions in levels of a broad range of atherogenic lipids and lipoproteins, including low-density lipoprotein (LDL) cholesterol, non–high-density lipoprotein cholesterol, triglycerides, apolipoprotein B, and lipoprotein(a). These findings were consistent with earlier studies of resmetirom.

From baseline to week 24, LDL cholesterol levels changed by -13.6% in the 80-mg and by -16.3% in the 100-mg resmetirom groups compared with 0.1% in the placebo group ($P < .001$).

More patients in the 100-mg group than in the 80-mg or placebo groups discontinued the trial due to adverse events (6.8% vs 1.8% and 2.2%, respectively). Diarrhea and nausea occurred more frequently in the resmetirom groups than in the placebo group.

Serious adverse events occurred with similar incidences across the 100-mg, 80-mg, and placebo groups (12.7%, 10.9%, and 11.5%, respectively).

Although to date the MAESTRO-NASH trial lacks clinical outcomes, over its planned duration of 54 months, investigators will accrue data on liver-related outcomes, including progression to cirrhosis. Likewise, long-term safety data will become available with the trial's completion.

Disclosure forms provided by the authors are available with the full text of the NEJM paper at www.NEJM.org. ■

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should be avoided in the esophagus and duodenum, as the clinical consequences of a leak can be devastating and endoscopic closure is notoriously challenging."

Dr. D'Souza and colleagues went on to discuss various non-exposed techniques, including submucosal tunneling and endoscopic resection and peroral endoscopic tunnel resection (STER/POET), device-assisted endoscopic full-thickness resection, and full-thickness resection with an over-the-scope clip with integrated snare (FTRD).

They highlighted how STER/POET encourages traction on the lesion and scope stability while limiting extravasation of luminal contents, and closure tends to be easier than with exposed EFTR. This approach should be reserved for tumors smaller than approximately 3-4 cm, however, with the update noting that lesions larger than 2 cm may present increased risk of incomplete resection. Similarly, device-assisted endoscopic full-thickness resection, which involves pulling or suctioning the lesion into the device, is also limited by lesion size, although fewer data are available to guide size thresholds.

"Further research into the efficacy of these resection techniques and the long-term outcomes in patients after endoscopic resection of SELs will be essential in standardizing appropriate resection algorithms."

FTRD, which involves "a 23-mm deep cap with a specially designed over-the-scope clip and integrated cautery snare," also lacks a broad evidence base.

"Although there has been reasonable clinical success reported in most case series, several factors should be considered with the use of the FTRD for SELs," the update cautions.

Specifically, a recent Dutch and German registry study of FTRD had an adverse event rate of 11.3%, with an approximate 1% perforation rate. More than half of the perforations were due to technical or procedural issues.

"This adverse event rate may improve as individual experience with the device is gained; however, data on this are lacking," the panelists wrote, also noting that lesions 1.5 cm or larger may carry a higher risk of incomplete resection.

Ultimately, the clinical practice update calls for a personalized approach to EFTR decision-making that considers factors extending beyond the lesion.

"The 'ideal' technique will depend on various patient and lesion characteristics, as well as the endoscopist's preference and available expertise," Dr. D'Souza and colleagues concluded.

"Further research into the efficacy of these resection techniques and the long-term outcomes in patients after endoscopic resection of SELs will be essential in standardizing appropriate resection algorithms."

This clinical practice update was commissioned and approved by AGA Institute. The investigators disclosed relationships with Olympus, Fujifilm, Apollo Endosurgery, and others. ■

Private Equity in GI

Dear colleagues,

In this issue of Perspectives we will explore the business of medicine. With changes in reimbursement models and healthcare regulation over the past decades, private practice gastroenterology has evolved. Many gastroenterologists are now employed or are part of larger consolidated organizations. A key part of this evolution has been the influx of private equity in GI. The impact of private equity is still being written, and while many have embraced this business model, others have been critical of its influence.

In this issue, Dr. Paul J. Berggreen discusses his group's experience with private equity and how it has helped improve the quality of patient care that they provide.

Dr. Michael L. Weinstein provides the counterpoint, discussing potential issues with the private equity model, and also highlighting an alternative path taken by his practice. An important topic for gastroenterologists of all ages. We welcome your experience with this issue. Please share with us on X @AGA_GIHN.


Dr. Ketwaroo

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

The Future of Medical Practice

BY PAUL J. BERGGREEN, MD

The future of medicine is being written as we speak. Trends that began in past decades have accelerated. Consolidation among massive hospital systems and health insurance conglomerates has gained momentum.

Physicians have been slow to organize and slower to mobilize. We spend our time caring for patients while national forces shape the future of our profession.

These trends have motivated many physicians to explore vehicles that allow them to remain independent. Creating business relationships with financial entities, including private equity, is one of those methods.


Dr. Berggreen

Before those models are explored, some background is instructive.

More than 100,000 doctors have left private practice and become employees of hospitals and other corporate entities since 2019. Today, approximately 75% of physicians are employees of larger healthcare entities — a record high.

This trend ought to alarm patients and policymakers. Research shows that independent medical practices often deliver better outcomes for patients than hospitals. Physician-owned practices also have lower per-patient costs, fewer preventable hospital admissions, and fewer re-admissions than their larger hospital-owned counterparts.

The business of medicine is very different than it was 40 years ago, when more than three in four doctors cared for patients in their own medical practices. The cost of managing a practice has surged. Labor, rent, and malpractice insurance have grown more expensive. Physicians have had to make significant investments in information technology, and electronic health records.

Medicare's reimbursement rates have not kept pace with these higher operational costs. In fact, Medicare payments to doctors have declined more than 25% in the last two decades after accounting for inflation.

By contrast, reimbursement for inpatient and outpatient hospital services as well as skilled nursing facilities has outpaced inflation since 2001.

Given these economic headwinds — and the mounting administrative and financial burdens that government regulation poses — many independent practitioners have concluded that they have little choice but to sell to larger entities like hospitals, health systems, or insurers.

If they do, they lose autonomy. Patients lose the personal touch an independent practice can offer.

To stay independent, many physicians are partnering with management services organizations (MSOs), which provide nonclinical services such as compliance, contracting, legal and IT support, cybersecurity, marketing, community outreach, recruiting assistance, billing, accounts payable, and guidance on the transition to value-based care.

MSOs are typically backed by investors: perhaps a public company, or a private equity firm. But it's important to note that the clinical entity — the practice — remains

Future *continued on following page*

Thinking Strategically About Gastroenterology Practice

BY MICHAEL L. WEINSTEIN, MD

Whether you are a young gastroenterologist assessing your career opportunities, or a gastroenterology practice trying to ensure your future success, you are likely considering how a private equity transaction might influence your options. In this column, I am going to share what I've learned and why my practice chose not to go the route of a private equity investment partner.


Dr. Weinstein

In 2018, Capital Digestive Care was an independent practice of 70 physicians centered around Washington. Private equity firms were increasingly investing in healthcare, seeking to capitalize on the industry's fragmentation, recession-proof business, and ability to leverage consolidation. Our leadership chose to spend a weekend on a strategic planning retreat to agree on our priorities and long-term goals. I highly recommend that you and/or your practice sit down to list your priorities as your first task.

After defining priorities, a SWOT (strengths, weaknesses, opportunities, and threats) analysis of your position today and what you project over the next decade will determine a strategy. There is a current shortage of more than 1400 gastroenterologists in the United States. That gives us a pretty powerful "strength." However, the consolidation of commercial payers and hospital systems is forcing physicians to accept low reimbursement and navigate a maze of administrative burdens. The mountain of regulatory, administrative, and financial functions can push physicians away from independent practice. Additionally, recruiting, training, and managing an office of medical personnel is not what most gastroenterologists want to do with their time.

The common denominator to achieve success with all of these practice management issues is size. So before providing thoughts about private equity, I recommend consolidation of medical practices as the strategy to achieving long-term goals. Practice size will allow physicians to spread out the administrative work, the cost of the business personnel, the IT systems, and the specialized resources. Purchasing power and negotiation relevance is achieved with size. Our priorities are taking care of our patients, our staff, and our practice colleagues. If we are providing high-value service and have a size relevant to the insurance companies, then we can negotiate value-based contracts, and at the end of the day, we will be financially well-off.

In contrast to the list of priorities a physician would create, the private equity fund manager's goal is to generate wealth for themselves and their investors. Everything else, like innovation, enhanced service, employee satisfaction, and great quality, takes a back seat to accumulating profit. Their investments are made with a life-cycle of 4-6 years during which money is deployed by acquiring companies, improving the company bottom

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separate from the MSO. Physicians retain control over clinical decision-making after partnering with an MSO.

Private equity is best viewed as a neutral financing mechanism that provides independent practices access to capital so they can build the business, clinical, and technological infrastructure to compete against the vertically integrated health systems that dominate medicine.

Private equity firms don't "acquire" independent practices. A partnership with a private equity–backed MSO is often what empowers a practice to resist acquisition by a larger hospital or healthcare system.

The experience of my own practice, Arizona Digestive Health, is instructive. We partnered with GI Alliance — a private equity-backed, gastroenterologist-led MSO — in 2019.

My physician colleagues and I have retained complete clinical autonomy. But we now have the financial and operational support we need to remain independent — and deliver better care for our patients.

For example, we led the development of a GI-focused, population-based clinical dashboard that aggregates real-time data from almost 3 million patients across 16 states who are treated by practices affiliated with GI Alliance.

By drawing on that data, we've been able to implement comprehensive care-management programs. In the case of inflammatory bowel disease, for instance, we've been able to identify the highest-cost, most at-risk patients and implement more proactive treatment protocols, including dedicated care managers and hotlines. We've replicated this model in other disease states as well.

This kind of ongoing, high-touch intervention improves patient outcomes and reduces overall cost by minimizing unplanned episodes of care — like visits to the emergency room.

It's not possible to provide this level of care in a smaller setting. I should know. I tried to implement a similar approach for the 55 doctors that comprise Arizona Digestive Health in Phoenix. We simply didn't have the capital or resources to succeed.

Our experience at Arizona Digestive Health is not an outlier. I have seen numerous independent practices in gastroenterology and other specialties throughout the country leverage the resources of private equity–backed MSOs to enhance the level of care they provide — and improve patient outcomes and experiences.

In 2022, the physician leadership of GI Alliance spearheaded a transaction that resulted in the nearly 700 physicians whose independent gastroenterology practices were part of the alliance to grow their collective equity stake in the MSO to more than 85%. Our independent physicians now have voting control of the MSO board of directors.

This evolution of GI Alliance has enabled us to remain true to our mission of putting patients first while enhancing our ability to shape the business support our partnered gastroenterology practices need to expand access to the highest-quality, most affordable care in our communities.

Doctors caring for patients in their own practices used to be the foundation of the US healthcare system — and for good reason. The model enables patients to receive more personalized care and build deeper, more longitudinal, more trusting relationships with their doctors. That remains the goal of physicians who value autonomy and independence.

Inaction will result in more of the same, with hospitals and insurance companies snapping up independent practices. It's encouraging to see physicians take back control of their profession. But the climb remains steep.

The easiest way to predict the future is to invent it. Doing so in a patient-centric, physician-led, and physician-owned group is a great start to that journey. ■

Dr. Berggreen is board chair and president of the American Independent Medical Practice Association. He is founder and president of Arizona Digestive Health, chief strategy officer for the GI Alliance, and chair of data analytics for the Digestive Health Physicians Association. He is also a consultant to Specialty Networks, which is not directly relevant to this article.

Read More!

Find more of these debates online at MDedge.com/gihepnews.perspectives.

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line profit through cost cutting or bolt-on acquisitions, increasing company profit distributions by adding leveraged debt to the corporate ledger, and then selling the companies often to another private equity fund. Physicians are trained to provide care to patients, and fund managers are trained to create wealth.

The medical practice as a business can grow over a career and provides physicians with top tier incomes. We are proud of the businesses we build and believe they are valuable. Private equity funds acquire medical practices for the future revenue and not the past results. They value a medical practice based on a multiple of the portion of future income the practice wants to sell. They ensure their future revenue through agreements that provide them management fees plus 25%-35% of future physician income for the current and all future physicians. The private equity company will say that the physicians are still independent but in reality all providers become employees of the company with wages defined by a formula.

The private equity–owned management services organization (MSO) controls decisions on carrier contracts, practice investments, purchasing, hiring, and the operations of the medical office. To get around corporate practice of medicine regulations, the ownership of the medical practice is placed in the hands of a single friendly physician who has a unique relationship to the MSO.

In my opinion, private equity is not the best strategy to achieve a successful medical practice, including acquiring the needed technology and human resources. It comes at a steep price, including loss of control and a permanent forfeiture of income ("the scrape"). The rhetoric professes that there will be income repair, monetization of practice value, and opportunity for a "second bite of the apple" when the private equity managers sell your practice to the next owner. Private equity's main contribution for their outsized gains is the capital they bring to the practice. Everything else they bring can be found without selling the income of future partners to create a little more wealth for current partners.

The long-term results of private equity investment in gastroenterology practices has yet to be written. The experience in other specialties is partly documented in literature but the real stories are often hidden behind non-disparagement and non-disclosure clauses. Several investigations show that private equity ownership of healthcare providers leads to higher costs to patients and payers, employee dissatisfaction, diminished patient access, and worse health outcomes. The Federal Trade Commission and Department of Justice have vowed to scrutinize private equity deals because of mounting evidence that the motive for profit can conflict with maintaining quality.

In 2019, Capital Digestive Care (CDC) chose Physicians Endoscopy as our strategic partner with the goal of separating and expanding our back-office functions into an MSO capable of providing business services to a larger practice and services to other practices outside of our own. Physicians Endoscopy has since been acquired by Optum/SCA. PE GI Solutions, the MSO, is now a partnership of CDC physician partners and Optum/SCA. Capital Digestive Care remains a practice owned 100% by the physicians. A Business Support Services Agreement defines the services CDC receives and the fees paid to the PE GI Solutions. We maintain MSO Board seats and have input into the operations of the MSO.

Consider your motivations and the degree of control you need. Do you recognize your gaps of knowledge and are you willing to hire people to advise you? Will your practice achieve a balance between the interests of older and younger physicians? Becoming an employed physician in a large practice is an option to manage the concerns about future career stability. Improved quality, expanded service offerings, clout to negotiate value-based payment deals with payers, and back-office business efficiency do not require selling yourself to a private equity fund. ■

Dr. Weinstein is a founder and now chief executive officer of Capital Digestive Care. He is a founder and past president of the Digestive Health Physicians Association, previous counselor on the Governing Board of the American Gastroenterological Association. He reports no relevant conflicts.

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Wearable Device Tracks IBD From Sweat

BY JIM KLING
MDedge News

FROM CROHN'S & COLITIS CONGRESS

LAS VEGAS — Measuring disease status in inflammatory bowel disease (IBD) patients generally requires invasive blood draws or procedures, but a novel wearable device shows initial promise at providing similar information from perspiration.

The device, in development by EnLiSense, can rapidly detect calprotectin, C-reactive protein (CRP), and interleukin-6 (IL-6), using miniaturized versions of biochemical lab tests.

Patient monitoring relies on identifying trends, whether biomarker levels are increasing or decreasing, according to Shalini Prasad, PhD, who presented the study during a poster session at the annual Crohn's & Colitis Congress®, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association. "In a blood test you don't get that unless you're willing to sample every month. That's the benefit [of the device]," said Dr. Prasad, professor of bioengineering at University of Texas at Dallas and a cofounder of EnLiSense.

The project grew out of the involvement of EnLiSense with the Biomedical Advanced Research Development Authority (BARDA). "We were tracking infections, and we were looking at inflammatory markers associated with infections: Cytokines and chemokines. We thought it was a natural pivot for us because the disease of inflammation is IBD," said Dr. Prasad.

The device need only be worn when the physician determines the disease is in a variable state. The patient "will wear it for the duration of time as determined by the clinician," said Dr. Prasad.


Dr. Prasad

The watch face–sized device, typically worn on the forearm, absorbs sweat and performs automated biochemical analysis independently, then beams its findings to the cloud. "What you get back is concentration [of inflammatory biomarkers]. It is essentially trend line reporting of how the concentration is fluctuating over time for markers," said Dr. Prasad.

The Crohn's and Colitis Foundation is supporting the company through its IBD Ventures program. EnLiSense is currently conducting a study tracking patients over 4 weeks to correlate biomarker concentrations in sweat with concentrations in stool.

A key remaining question is how long the device should be worn and during what clinical periods. The technology has the potential to provide too much information. "Just figuring the balance. We're trying to find the right spot where it makes sense for both the clinician and the patient. This is something that is a work in progress. We don't want this to be just like any other consumer wearable which gives you something but you're not sure what it means," said Dr. Prasad.

The study included 33 patients with IBD who were monitored between 40 and 130 minutes. The device measured levels of CRP, IL-6, and calprotectin. Serum samples were also measured the same day.

The researchers found higher levels of calprotectin among patients with active disease in perspiration ($P = .0260$), serum ($P = .022$), and in fecal samples ($P = .0411$). There were no significant differences between patients who are active and those in remission with respect to CRP levels in perspiration or serum, or IL-6 in perspiration. Serum Il-6 levels were higher in those with active disease.

There was no significant difference between serum and sweat calprotectin levels among patients who were active or in remission, but the median expression of IL-6 in perspiration was higher in the active group ($P = .0016$). In the active group, calprotectin was elevated in sweat, serum, and stool.

Levels of calprotectin measured in perspiration correlated with levels in the serum (R2 = 0.7195), as did CRP (R2 = 0.615) and IL-6 (R2 = 0.5411).

Treating to Target

The poster caught the interest of Jeremiah Faith, PhD, who attended the session and was asked to comment. "I think patients want to know what's happening [with their disease], and we could probably give better care if we know day to day the status of someone, especially because every time we test them we get a point in time, but the reality is probably that people are kind of wavy, and knowing the wave is much better," he said.

"We're trying to find the right spot where it makes sense for both the clinician and the patient. This is something that is a work in progress. We don't want this to be just like any other consumer wearable."

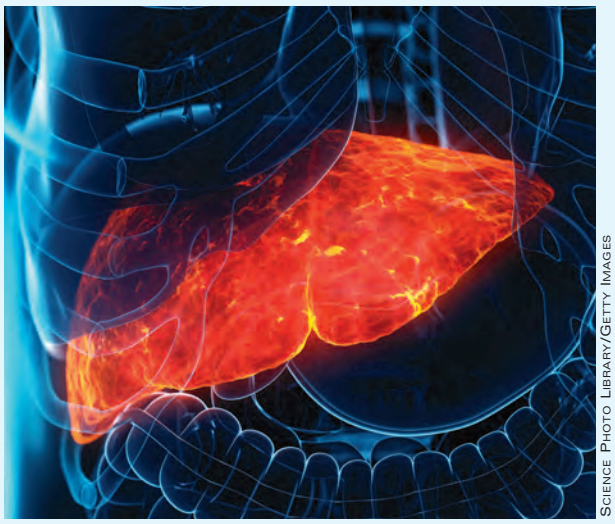
He noted that there was not a strong separation between mean perspiration calprotectin values, but he said the ability to take frequent measurements could overcome that weakness. "The difference between active and remission is not as drastic as what you'd see from blood, for example. But it's the same thing with your watch. Your watch is a really poor sensor of what your heartbeat is doing, but if you measure it every few seconds, and you average over a long period of time, it can actually more be more [accurate]. So there's a lot of potential for this," said Dr. Faith, associate professor of genetics and genomic sciences at the Icahn School of Medicine at Mount Sinai in New York.

If perfected, the device could help efforts at treating to target, in which therapies are adjusted to achieve minimal disease. Currently, physicians are forced to adjust doses or change therapies based on infrequent testing. "If this is accurate ... maybe at some point we will have the tools to be smarter about it," said Dr. Faith.

Dr. Prasad is a cofounder of EnLiSense. Dr. Faith has no relevant financial disclosures. ■

Iron Overload in Non-HFE Liver Disease: Not All Iron Is Ready to Strike

BY PAUL MARTIN, MD, AND LAWRENCE S. FRIEDMAN, MD



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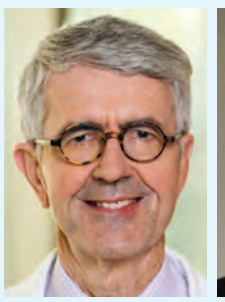
Pathological iron overload with end-organ damage in hemochromatosis occurs in individuals who are homozygous for the major mutation C282Y. Phenotypic hemochromatosis occurs much less frequently in compound heterozygotes with one C282Y mutation and one H63D mutation. Iron overload can be confirmed by magnetic resonance imaging, which shows a loss of signal intensity in affected tissues and avoids the need for liver biopsy.

The serum ferritin level, an acute phase reactant, may be elevated for reasons other than iron overload, including infection and malignancy; in such cases, the iron saturation is usually normal. In patients with liver disease, iron overload is not restricted to patients with genetic hemochromatosis. In nonalcoholic fatty liver disease (NAFLD), up to one-third of patients have an elevated iron saturation (> 45%) and an elevated serum ferritin level. Iron accumulation in NAFLD can occur in hepatocytes, the reticuloendothelial system, or both. Deposition of iron in the reticuloendothelial system has been implicated in more severe liver disease (steatohepatitis and fibrosis) in NAFLD. Hepatic iron accumulation is also frequent in alcohol-associated liver disease. In chronic hepatitis B and C, accumulation of hepatic iron is also recognized.

In any patient with chronic liver disease, an elevated serum ferritin or an elevated iron saturation should prompt testing for HFE mutations to exclude hemochromatosis. ■

Dr. Martin is chief of the division of digestive health and liver diseases at the Miller School of Medicine, University of Miami, Miami, Florida, where he is the Mandel Chair of Gastroenterology. Dr. Friedman is the Anton R. Fried, MD, Chair of the department of medicine at Newton-Wellesley Hospital in Newton, Massachusetts, and assistant chief of medicine at Massachusetts General Hospital, and a professor of medicine at Harvard Medical School and Tufts University School of Medicine, all in Boston.

The authors disclosed no conflicts. Previously published in Gastro Hep Advances. 2023 Oct 12. doi: 10.1016/j.gastha.2023.10.004).



Dr. Martin

Dr. Friedman

AGA Tech Summit Focuses on Accelerating Innovation

The AGA Tech Summit is building on the success of past summits and moving in a new direction. The reimagined summit will accelerate innovation by bringing together MedTech startups, innovators, investors, and leaders in the field.

"It's a new world out there. The Tech Summit now reflects the new direction AGA is taking in innovation," said Lawrence R. Kosinski, MD, AGA at-large councilor for development and growth. "We want to help GI innovators successfully navigate the innovation lifecycle from start to finish and bring new technologies to market."

"The Tech Summit now reflects the new direction AGA is taking in innovation. We want to help GI innovators successfully navigate the innovation lifecycle from start to finish and bring new technologies to market."

The Tech Summit will take place April 11-12 in Chicago at MATTER, located at the Merchandise Mart. MATTER supports healthcare startups at all stages of growth and brings together industry executives, entrepreneurs, and investors to accelerate innovation, advance care, and improve lives.

Highlights of the Tech Summit include:

- Keynote addresses from leaders in the field of GI innovation.
- Panel discussions with venture capital strategists.
- The Shark Tank Pitch Competition featuring emerging GI technologies.
- Multiple opportunities to network innovators, investors, and leaders in the field.
- One-on-one consultations with venture capital firms.

Early bird registration is by March 11, standard registration is through April 8. For more information on the Tech Summit, visit gastro.org/AGAtech. ■

Immediate clinical implications

CRC risk *from page 1*

signs and symptoms of colorectal cancer, such as iron deficiency anemia and rectal bleeding, that are otherwise unexplained, including for those under age 45," he said.

We also should make "sure that all people eligible for screening — at age 45 and older — have every opportunity to get screened for colorectal cancer," Dr. Gupta added.

The review was published online in *Clinical Gastroenterology and Hepatology* (2023 Dec 9. doi: 10.1016/j.cgh.2023.11.040).

Dr. Gupta

Tracking Birth Cohort Trends

CRC rates have increased in the United States among people born since the early 1960s, the authors wrote.

Generation X (individuals born in 1965-1980) experienced an increase in EOCRC, and rates subsequently increased in this generation after age 50. Rates are 1.22-fold higher among people born in 1965-1969 and 1.58-fold higher among those born 1975-1979 than among people born in 1950-1954.

Now rates are also increasing across younger generations, particularly among Millennials (individuals born in 1981-1996) as they enter mid-adulthood. Incidence rates are 1.89-fold higher among people born in 1980-1984 and 2.98-fold higher among those born in 1990-1994 than among individuals born in 1950-1954.

These birth cohort effects are evident globally, despite differences in population age structures, screening programs, and diagnostic strategies around the world. Due to this ongoing trend, physicians anticipate that CRC rates will likely continue to increase as higher-risk birth cohorts become older, the authors wrote.

Notably, four important shifts in CRC incidence are apparent, they noted. First, rates are steadily increasing up to age 50 and plateauing after age 60. Rectal cancers are now predominant through ages 50-59. Rates of distant-stage disease have increased most rapidly among ages 30-49 and more slowly decreased among ages 60-79 compared with those of local-stage disease. In addition, the increasing rates of EOCRC have been observed across all racial and ethnic groups since the early 1990s.

These shifts led to major changes in the types of patients diagnosed with CRC now vs 30 years ago, with a higher proportion being patients younger than 60, as well as Black, Asian or Pacific Islander, American Indian/Alaska Native, and Hispanic patients.

The combination of age-related increases in CRC and birth cohort–related trends will likely lead to substantial increases in the number of people diagnosed with CRC in coming years, especially as Generation X patients move into their 50s and 60s, the authors wrote.

Research and Clinical Implications

Birth cohort CRC, including increasing EOCRC incidence, likely is driven by a range of influences, including demographic, lifestyle, early-life, environmental, genetic, and somatic factors, as well as interactions among them, the authors noted. Examples within these broad categories include male sex, food insecurity, income inequality, diabetes, alcohol use, less healthy dietary patterns, in utero exposure to certain medications, and microbiome concerns such as early-life antibiotic exposure or dysbiosis.

"From a research perspective, this means that we need to think about risk factors and mechanisms that are associated with birth cohorts, not just age at diagnosis," Dr. Gupta said. "To date, most studies of changing epidemiology have not taken into account birth cohort, such as whether someone is Generation X or later versus pre-Baby Boomer."

Although additional research is needed, the epidemiology changes have several immediate clinical implications, Dr. Gupta said. For those younger than 45, it is critical to raise awareness about the signs and symptoms of CRC, such as hematochezia, iron deficiency anemia, and unintentional weight loss, as well as family history.

For ages 45 and older, a major focus should be placed on increasing screening participation and follow-up after abnormal results, addressing disparities in screening participation, and optimizing screening quality.

In addition, as CRC incidence continues to increase, health systems and policymakers should ensure every patient has access to guideline-appropriate care and innovative clinical trials, the authors wrote. This access may be particularly important to address the increasing burden of rectal cancer, as treatment approaches rapidly evolve toward more effective therapies, such as neoadjuvant chemotherapy and radiation prior to surgery, and with less-morbid treatments on the horizon, they added.

Dr. Ogino

'An Interesting Concept'

"Birth cohort CRC is an interesting concept that allows people to think of their CRC risk according to their birth cohort in addition to age," Shuji Ogino, MD, PhD, chief of the Molecular Pathological Epidemiology program at Brigham & Women's Hospital, Boston, Massachusetts, told *GI & Hepatology News*.

Dr. Ogino, who wasn't involved with this study, serves as a member of the cancer immunology and cancer epidemiology programs at the Dana-Farber Harvard Cancer Center. In studies of EOCRC, he and colleagues have found various biogeographical and pathogenic trends across age groups.

"More research is needed to disentangle the complex etiologies of birth cohort CRC and early-onset CRC," Dr. Ogino said. "Tumor cells and tissues have certain past and ongoing pathological markers, which we can detect to better understand birth cohort CRC and early-onset CRC."

The study was funded by several National Institutes of Health/National Cancer Institute grants. Dr. Gupta disclosed consulting for Geneoscopy, Guardant Health, Universal Diagnostics, InterVenn Bio, and CellMax. Another author reported consulting for Freenome, Exact Sciences, Medtronic, and Geneoscopy. Dr. Ogino reported no relevant financial disclosures. ■

FDA Expands Dupilumab for EoE to Younger Children

BY MEGAN BROOKS

The US Food and Drug Administration (FDA) has approved dupilumab (Dupixent, Regeneron/Sanofi) for the treatment of eosinophilic esophagitis (EoE) in children aged 1-11 years and weighing ≥ 15 kg. It is the first and only medicine approved to treat these patients.

The FDA previously approved the drug for EoE in persons aged 12 years or older and weighing ≥ 40 kg in May 2022.

Dupilumab is a monoclonal antibody that acts to inhibit part of the inflammatory pathway.

The FDA approval of dupilumab for younger children is based on results from the phase 3 randomized, double-blind, placebo-controlled EoE KIDS trial, which had two parts.

Part A was a 16-week double-blind treatment period that evaluated the safety and efficacy of dupilumab in a tiered weight-based dosing schema.

At 16 weeks, 66% of children who received higher-dose dupilumab at tiered dosing regimens based on weight achieved histologic disease remission (six or fewer eosinophils/high-power field), which was the primary endpoint, compared with only 3% of children who received placebo.

In addition, a greater decrease in the proportion of days with one or more signs of EoE according to the Pediatric EoE Sign/Symptom Questionnaire caregiver version (PESQ-C) was observed in children treated with dupilumab at 16 weeks compared with placebo.

Part B was a 36-week extended active treatment period in which eligible children from part A in the dupilumab group continued to receive their dose level and those in the placebo group in part A switched to active treatment.

Histologic remission was sustained at week 52 in 53% of children treated with dupilumab in parts A and B. Histologic remission was also achieved at week 52 in 53% of children who switched to dupilumab from placebo in part B.

The safety profile of dupilumab observed through 16 weeks in these children was generally in line to that seen through 24 weeks in persons aged 12 years or older with EoE.

The most common adverse events observed with dupilumab were injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. ■

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NEWS FROM THE FIELD AND AGA

EXPERT PERSPECTIVES

HEALTH POLICY, TECH, AND COSTS OF CARE

CONFERENCE COVERAGE

FEATURES, QUIZZES, AND MORE

AGA Sharpens Focus on Women

As the number of women in gastroenterology grows, so does AGA's portfolio of programs focused on maximizing the role of women in GI.

"Women continue to face unique barriers to leadership including gender bias, lack of role models, maternal discrimination, and lack of equal consideration for opportunities," notes AGA President Barbara Jung, MD, AGAF. "AGA sits in a unique position where we can influence changes in academia and practice to improve the field for all women and particularly enhance women leaders."

A tangible way AGA supports female leadership and career advancement is the Women in GI Regional Workshops. Throughout 2024, these workshops provide opportunities for networking, business and financial education training, burnout prevention strategies, and career advice.

Bigger picture, AGA's Gender Equity Framework paints a compelling vision for the future in six domains:

- **Bias & gender disparities:** Academic institutions, healthcare systems, and practices establish regular systems of equity reviews and eradicate institutional gender disparities and bias.
- **Leadership & career advancement:** Equitable access to leadership in the field and professional GI societies for the benefit of medicine, research, and patient care.
- **Wellness & balance:** Women in GI experience balanced integration of family, work, community, health, and professional growth.
- **Retention & recruitment:** GI is the leading specialty for women in medicine and a sustainable career where women grow and thrive.
- **Mentorship & sponsorship:** The benefits of mentorship and sponsorship are universally recognized and incentivized in GI institutions and practices.
- **Recognition:** Equitable recognition of the achievements and contributions of women in GI.

In the coming years, AGA committees will collaborate with the AGA Women's Committee to achieve the vision laid out in the AGA Gender Equity Framework. Thank you to the AGA Women's Committee, which created the framework, under the leadership of chair Aimee Lucas, MD, MS, AGAF, and within the auspices of the AGA Equity Project (gastro.org/equity). ■

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

AGA supports female leadership and career advancement through Women in GI Regional Workshops. These workshops provide opportunities for networking, business and financial education training, burnout prevention strategies, and career advice.

Win! CMS Reins In Prior Authorization

According to a rule issued by the US Centers for Medicare & Medicaid Services (CMS), starting in 2026, **health plans must decide on prior authorization requests within 72 hours for an expedited request or 7 days for non-urgent appeals**.

The rule also requires plans to provide a detailed rationale for a denial and include metrics on denials and approvals.

AGA and our allies in the physician community have aggressively advocated that Congress and the Administration address prior authorization, which slows patient access to care and contributes to physician burnout.

The rule applies to Medicare, Medicare Advantage (MA), Medicaid, Children's Health Insurance Plans (CHIP), and qualified health plans on the exchange.

Thank you to our advocates who called on policymakers to take action to ensure patients receive care in a timely manner. ■

AGA Research Scholar Awards Advance the GI Field

The AGA Research Foundation plays an important role in medical research by providing grants to young scientists at a critical time in their career. AGA's flagship award is the Research Scholar Award, which provides career development support for young investigators in gastroenterology and hepatology research. In the last 10 years, the AGA Research Foundation has funded 63 young scientists through a Research Scholar Award grant.

"The AGA Research Scholar Award offers an unmatched opportunity to pursue the type of high-impact scientific work that allows a junior investigator … to achieve the necessary momentum to create a nationally competitive research program."

"I want to express my sincere gratitude to the AGA Research Foundation and its benefactors. At this fragile and critical juncture, the AGA Research Scholar Award offers an unmatched opportunity to pursue the type of high-impact scientific work that allows a junior investigator such as myself to achieve the necessary momentum to create a nationally competitive research program," states Alexander Nguyen, MD, PhD, the Regent of the University of California, Los Angeles, 2023 AGA Research Scholar Award recipient.

Funded by the generosity of donors, the AGA Research Foundation's research award program ensures that we are building a community of researchers whose work serves the greater community and benefits all our patients.

Dr. Nguyen

By joining others in supporting the AGA Research Foundation, you will ensure that young researchers have opportunities to continue their life-saving work. Your tax-deductible contribution supports the foundation's research award program, including the Research Scholar Award, which ensures that studies are funded, discoveries are made, and patients are treated. Learn more or make a contribution at www.foundation.gastro.org. ■

BCBSMA Rolls Back Restrictive Anesthesia Policy

In a significant victory for patients and healthcare providers, Blue Cross Blue Shield of Massachusetts (BCBSMA) has officially postponed its restrictive anesthesia policy until further notice. The change is retroactive to Jan. 1, 2024, so no claims will be rejected for payment.

The decision follows intense advocacy efforts by a coalition that included AGA and its fellow GI societies, the American Society of Anesthesiologists, and the American College of Surgeons, with the Massachusetts Gastroenterology Association demonstrating exceptional leadership and the Massachusetts Society of Anesthesiologists persevering throughout the process.

BCBSMA heeded the coalition's warnings about the potential impact on cancer screening access and patient choice in GI care.

Physician leaders representing the societies played a crucial role in meetings with BCBSMA, contributing to this positive outcome. Member engagement, including contacting legislators, media outreach, and participation in the #Noto154 campaign, had a substantial impact.

BCBSMA informed the societies that all claims will be paid; however, documentation will still be required for patients presenting with classifications ASA 1 and ASA 2.

Providers may download a list (http://tinyurl.com/mrxfkxx9) of commonly used diagnosis codes documented with the administration of propofol.

AGA encourages members to still be mindful that BCBSMA will be monitoring the use of these codes for propofol administration.

Members can see BCBSMA policy document 154 (http://tinyurl.com/bdx6jv3b) for the complete list of diagnosis codes that support use of Monitored Anesthesia Care (MAC) in the outpatient setting.

The societies have requested that BCBSMA provide education to providers on this requirement.

AGA intends to closely monitor developments to ensure similar policies are not introduced nationally. ■

A 'critical challenge' to health systems

Telephone *from page 1*

doi: 10.1001/jamainternmed.2018.4637), but have not been compared for efficacy in terms of communicating updated colonoscopy intervals.

The trial's aim was to inform low-risk patients of the recommended interval update from 5 years — used since the 1990s — to 7-10 years. Given a choice, more patients opted to transition to the 10-year surveillance interval in the telephone (37%) and secure messaging arms (32.%) compared with mailed-letter arm (18.9%).

In addition to telephone and secure messaging outreach, factors positively associated with adoption of the 10-year interval were a positive fecal immunochemical test–based index colonoscopy and increasing age. Patients with these characteristics may be biased toward avoiding colonoscopy if not medically necessary, the authors conjectured.

Dr. Lee

"We gave all our patients an option to either extend their surveillance interval to current guideline recommendations or continue with their old interval. … Patients really appreciated having a choice."

Inversely associated factors included Asian or Pacific Islander race (odds ratio [OR], 0.58), Hispanic ethnicity (OR, 0.40), and a higher Charlson comorbidity score of 2 vs 0 (OR, 0.43).

Possible explanations for the race and ethnicity associations include gaps in culturally competent care, lack of engagement with the English-based outreach approaches, and medical mistrust, the authors said.

"In this study, we gave all our patients an option to either extend their surveillance interval to current guideline recommendations or continue with their old interval, and some chose to do that," Dr. Lee said in an interview. "Patients really appreciated having a choice and to be informed about the latest guideline changes."

"A critical challenge to health systems is how to effectively de-implement outdated surveillance recommendations for low-risk patients who have a 5-year follow-up interval and potentially transition them to the recommended 7- to 10-year interval," Dr. Lee and colleagues wrote.

More than 5 million surveillance colonoscopies are performed annually in US patients with a history of adenomas, the main precursor lesion for colorectal cancer, the authors noted.

With the recent guidelines issued in 2020 by the US Multi-Society Task Force on Colorectal Cancer lengthening the follow-up interval to 7-10 years (Gastroenterol. 2020 Feb. doi: 10.1053/j.gastro.2019.10.026), physicians are being advised to reevaluate low-risk patients previously scheduled with 5-year surveillance and provide an updated recommendation for follow-up.

Study Details

The three-arm pragmatic randomized trial was conducted in low-risk patients 54-70 years of age with one or two small (< 10 mm) tubular adenomas at baseline colonoscopy. Participants due for 5-year surveillance in 2022 were randomly assigned to one of three outreach arms: telephone (n = 200), secure messaging (n = 203), and mailed letter (n = 201). Stratified by age, sex, race, and ethnicity, participants could change their assigned interval to 10 years or continue with their previously scheduled 5-year interval.

As to economic considerations, the authors said that telephone may be the costliest form of outreach in terms of staffing resources. "We don't know because we did not conduct a formal cost-effectiveness analysis," Dr. Lee said. "However, we do know phone outreach requires a lot of personnel effort, which is why we also explored the less costly option of secure messaging/email."

But based on the findings, telephone outreach would be a reasonable approach to update patients on post-polypectomy surveillance guideline changes if secure messaging or text messaging isn't available, he added.

Downsides to Retroactive Changes?

Commenting on the study but not involved in it, Nabil M. Mansour, MD, an assistant professor and director of the McNair General GI Clinic at Baylor College of Medicine in Houston, Texas, noted that unlike Kaiser Permanente, his center decided against an overall effort to switch patients colonoscopied before the release of the new guidelines over to the new interval.

Dr. Mansour

"Several of our physicians may have chosen to recommend a 5-year interval specifically for a variety of reasons and we felt … making a blanket change to everyone's interval retrospectively might create confusion and frustration."

"Several of our physicians may have chosen to recommend a 5-year interval specifically for a variety of reasons and we felt going back, and making a blanket change to everyone's interval retrospectively might create confusion and frustration and might actually delay the colonoscopies of some patients for which their doctors had a very good, legitimate reason to recommend a 5-year interval," he said in an interview with *GI & Hepatology News*.

Dr. Mansour added that no difficulties were encountered in getting patients to agree to a 10-year interval. In his view telephone communication or in-person clinic visits are likely the most effective ways but both are more labor-intensive than automated patient portal messages. "I do not think traditional snail mail is effective." His clinic uses automatic EMR reminders.

Offering another perspective on the study, Aditya Sreenivasan, MD, a gastroenterologist at Northwell Health in New York City, said his center has not reached out to correct the old intervals. "When I see a patient who previously had a colonoscopy with another physician, I always follow the previous recommendation for when the next colonoscopy should be, regardless of whether or not it technically meets guideline recommendations," he told this news organization. "I do this because I was not there during the procedure and am not aware of any circumstances that would require a shorter interval that may not be apparent from the report."

Dr. Sreenivasan

"I think having a conversation with the patient directly is a much better way to communicate this information as it allows the patient to ask and answer questions. Things like tone of voice can provide reassurance that one cannot get via email."

While he agrees with the new guidelines, Dr. Sreenivasan is "not sure if retroactively changing intervals is beneficial to patients, as the presence of guidelines may subconsciously influence the behavior of the endoscopist at the time of the procedure. For example, if a patient has a technically challenging colonoscopy and the endoscopist is running late, the endoscopist may drop their guard once they find a polyp and miss one ot two additional small polyps that they would have spent more time looking for if they knew their next one would be in 10 years instead of 5."

As for notification method, despite the logistical downside of taking dedicated staff time to make telephone calls, Dr. Sreenivasan said, "I think having a conversation with the patient directly is a much better way to communicate this information as it allows the patient to ask and answer questions. Things like tone of voice can provide reassurance that one cannot get via email."

Looking to the future, the study authors acknowledged that combinations of initial and reminder outreach approaches — for example, a mailed letter followed by secure message or telephone call — could potentially yield higher response rates and/or adoption rates than they observed. And a longer follow-up period with additional reminders may have produced higher yields. Additional studies are needed to optimize outreach approaches and to understand patient barriers to adopting the new guideline recommendations in different healthcare settings.

The study was supported by a Delivery Science grant from the Kaiser Permanente Northern California. The authors disclosed no conflicts of interest. Dr. Mansour and Dr. Sreenivasan disclosed no conflicts of interest relevant to their comments. ■

No-Biopsy Approach to Celiac Disease Diagnosis Appears Effective for Select Adult Patients

BY CAROLYN CRIST
MDedge News

FROM GASTROENTEROLOGY

Select adult patients with immunoglobulin A–tissue transglutaminase antibody levels (IgA-tTG) greater than or equal to 10 times the upper limit of normal (ULN) and a moderate to high pretest probability of celiac disease could be diagnosed without undergoing invasive endoscopy and duodenal biopsy, according to a new study.

Current international guidelines recommend duodenal biopsies to confirm a celiac disease diagnosis in adult patients, but growing evidence suggests invasive procedures may not be needed, the authors wrote.

"Our study confirms the high accuracy of serology-based diagnosis of coeliac disease in select adult patients," said Mohamed G. Shiha, MBBCh, MRCP, lead author and a clinical research fellow in gastroenterology at Sheffield Teaching Hospitals in the United Kingdom.

"This no-biopsy approach could lead to a shorter time to diagnosis, increased patient satisfaction, and reduced healthcare costs," he said.

The study was published online in *Gastroenterology* (2024 Jan 4. doi: 10.1053/j.gastro.2023.12.023).

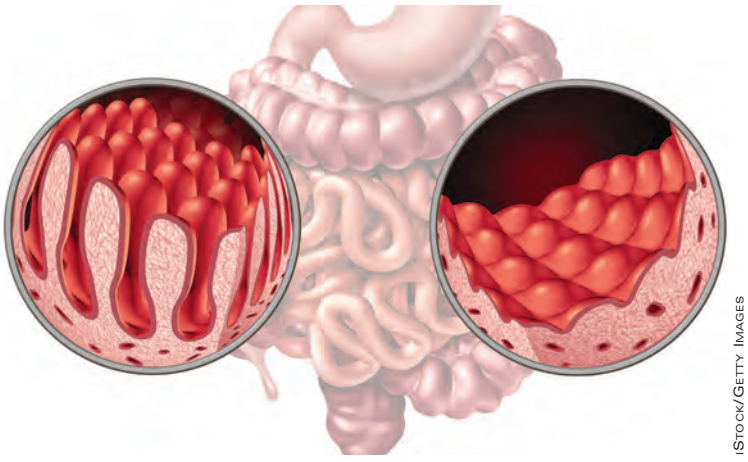
Evaluating the No-Biopsy Approach

Dr. Shiha and colleagues conducted a systematic review and meta-analysis to evaluate the accuracy of a no-biopsy approach for diagnosing celiac disease in adults. They looked for studies that reported the sensitivity and specificity of IgA-tTG ≥ 10xULN compared with duodenal biopsies (with a Marsh grade ≥ 2) in adults with suspected celiac disease.

The research team used a bivariate random-effects model to calculate the summary estimates of sensitivity, specificity, and positive and negative likelihood ratios. Then the positive and negative likelihood ratios were used to calculate the positive predictive value (PPV) of the no-biopsy approach across different pretest probabilities of celiac disease.

Among 18 studies with 12,103 participants from 15 countries, the pooled prevalence of biopsy-proven celiac disease was 62%. The proportion of patients with IgA-tTG ≥ 10xULN was 32%.

The summary sensitivity of IgA-tTG ≥ 10xULN was 51%, and the summary specificity was 100% for the diagnosis of celiac disease. The positive and negative likelihood ratios were 183.42 and 0.49, respectively. The area under the summary receiver operating characteristic curve was 0.83.



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Overall, the PPV of IgA-tTG ≥ 10xULN to identify patients with celiac disease was 98%, which varied according to pretest probability of celiac disease in the studied population. Specifically, the PPV was 65%, 88%, 95%, and 99% if celiac disease prevalence was 1%, 4%, 10%, and 40%, respectively. The 40% prevalence represents the lower confidence interval of the pooled prevalence from the included studies, the authors noted.

"We provided PPV estimates of IgA-tTG ≥ 10xULN for common pretest probabilities of coeliac disease to aid clinicians and patients in reaching an informed decision on a no-biopsy diagnosis based on the best available evidence," the authors wrote.

Considering Additional Factors

Due to the increased accuracy of serological tests, pediatric guidelines have adopted a no-biopsy approach, the authors wrote. Children with IgA-tTG ≥ 10xULN and positive serum endomysial antibodies (EMA) can be diagnosed with celiac disease without biopsy.

However, the no-biopsy approach remains controversial for diagnosing adult patients and requires additional study, the authors wrote. They noted a limitation that all included studies were conducted in secondary and tertiary care settings and excluded patients with known celiac disease or on a gluten-free diet, so the results may not be generalizable to primary care settings.

In addition, relying on serology testing alone could lead to potential false-positive diagnoses, unnecessary dietary restriction, and negative effects on patients' quality of life, the authors wrote.

At the same time, duodenal biopsy may not always be accurate because of inadequate sampling and could result in false-negative histology. The no-biopsy approach could mitigate this potential risk, the authors noted.

"This study systematically collates the growing data supporting the accuracy of antibody testing to diagnose celiac disease," said Benjamin Lebwohl, MD, AGAF, professor of medicine and epidemiology at Columbia University Medical Center and director of clinical research for the Celiac Disease Center at Columbia University, New York. Dr. Lebwohl wasn't involved with this study.

"We have historically relied on duodenal biopsy to confirm the diagnosis of celiac disease, and the biopsy will still have a central role in most cases in the foreseeable future," he said. "But as we hone our understanding of antibody testing, one day we may be able to accept or even recommend a biopsy-free approach in select patients."

Two authors reported grant support from the National Institute for Health and Care Research and National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Shiha reported speaker honorarium from Thermo Fisher. Dr. Lebwohl reported no relevant disclosures. ■

In Refractory IBD, Combination Therapies Appear Safe, Effective

BY JIM KLING
MDedge News

FROM CROHN'S & COLITIS CONGRESS

LAS VEGAS — In the treatment of inflammatory bowel disease, combinations of biologics or a biologic and tofacitinib appear to be generally safe and effective, according to a new systematic review and meta-analysis. The study updates a meta-analysis published in 2022, which included 13 studies. The new work included 23 studies that looked at eight different combinations.

There is a potential concern that the high adverse event rates seen in biologics could be compounded when they are used in combination, according to Ali Osman, MD, who presented the results at a poster session at the Crohn's & Colitis Congress®, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association. "Theoretically, you should have more side effects or more serious side effects, but interestingly we didn't find major side effects. I think the key message is that the combinations of biologic agents are promising in terms of efficacy. It doesn't lead to major adverse events," said Dr. Osman, an instructor at Washington University School of Medicine in St. Louis, Missouri.


Dr. Osman

"Our most effective [combination] in terms of response and remission was a combination of ustekinumab and an anti-TNF agent with a combined rate of 81.6%."

Although the study did not directly compare the combinations, it did find potential differences in efficacy. "Our most effective [combination] in terms of response and remission was a combination of ustekinumab and an anti-TNF agent with a combined rate of 81.6%. Our lowest adverse events rate were [with the combination of] tofacitinib and vedolizumab," said Dr. Osman.

The research is a useful update, according to David T. Rubin, MD, AGAF. "This has been explored before, but this is a nice effort to describe and try to compare studies of combination biological therapies or biologicals combined with [the JAK inhibitor]. This is to further explore the efforts being made to break the therapeutic ceiling by combining mechanisms, treat IBD and extra-intestinal manifestations with multiple agents simultaneously, and to explore novel treatment strategies," said Dr. Rubin, director of the Inflammatory Bowel Disease Center at University of Chicago Medicine.

He noted that the meta-analysis is limited by heterogeneity among the studies, many of which were case series that had been re-analyzed. The update included some prospective proof-of-concept studies of interest that were not in the earlier meta-analysis, including VEGA (anti-IL13 guselkumab plus anti-TNF golimumab versus either drug alone), and EXPLORER (vedolizumab, adalimumab, methotrexate), as well as a study of infliximab combined with natalizumab.


Dr. Rubin

"This has been explored before, but this is a nice effort to describe and try to compare studies of combination biological therapies or biologicals combined with [the JAK inhibitor]."

"We await the prospective trials of dual-targeted therapies that will undoubtedly include thoughtful combinations," said Dr. Rubin.

The review included 23 studies that had a minimum of two patients treated with a combination of two biologics or a biologic and tofacitinib. The biologics included the anti-TNF antibodies adalimumab, certolizumab pegol, golimumab, and infliximab; as well as guselkumab, natalizumab, ustekinumab, and vedolizumab. Overall, the studies included 531 patients who underwent 543 therapeutic trials, using eight different combinations.

The highest pooled clinical response observed was 81.6% with ustekinumab combined with an anti-TNF agent (P = .04, 9 studies, 44 therapeutic trials), which also had the highest remission rate of 64.2% (P = .03).

For the treatment of Crohn's disease, the highest pooled clinical response and remission rates were also seen with ustekinumab combined with an anti-TNF agent (8 studies, 29 therapeutic trials), at 91.6% (P = .28). In ulcerative colitis, vedolizumab plus ustekinumab had the highest pooled clinical response rate at 100.0% (P = 1.00; 4 studies, 4 treatment trials) and ustekinumab plus an anti-TNF agent F at 100.0% (P = 1.00; 4 studies, 5 treatment trials).

Tofacitinib combined with vedolizumab had the lower adverse event rate (12.5%; P = .10; 8 studies, 76 treatment trials) followed by ustekinumab and an anti-TNF agent (12.7%; P = .08; 9 studies, 43 treatment trials) and tofacitinib plus anti-TNF (13.0%; 6 studies, 27 treatment trials).

Other combinations included guselkumab plus ant-TNF (1 study; clinical response, 69.0%), natalizumab plus an anti-TNF agent (1 study, clinical response, 36.5%), tofacitinib plus an anti-TNF agent (5 studies, clinical response, 71.6%), tofacitinib plus ustekinumab (5 studies, clinical response, 70.8%), tofacitinib plus vedolizumab (8 studies, clinical response, 52.7%), vedolizumab plus an anti-TNF agent (13 studies, clinical response, 62.8%), and vedolizumab plus ustekinumab (12 studies, clinical response, 79.3%).

Dr. Osman has no relevant financial conflicts of interest. Dr. Rubin has received grant support from Takeda, and served as a consultant for AbbVie, Bristol-Myers Squibb, Janssen, Lilly, Pfizer, and Takeda. ■

The Breakthrough Drug Whose Full Promise Remains Unrealized

Celebrating a decade of sofosbuvir for hepatitis C

BY NANCY S. REAU, MD, AGAF

Prior to 2013, the backbone of hepatitis C virus (HCV) therapy was pegylated interferon (PEG) in combination with ribavirin (RBV). This year-long therapy was associated with significant side effects and abysmal cure rates. Although efficacy improved with the addition of first-generation protease inhibitors, cure rates remained suboptimal and treatment side effects continued to be significant.

Dr. Reau

Clinicians and patients needed better options and looked to the drug pipeline with hope. However, even among the most optimistic, the idea that HCV therapy could evolve into an all-oral option seemed a relative pipe dream.

The Sofosbuvir Revolution Begins

The Liver Meeting held in 2013 changed everything.

Several presentations featured compelling data with sofosbuvir, a new polymerase inhibitor that, when combined with RBV, offered an all-oral option to patients with genotypes 2 and 3, as well as improved efficacy for patients with genotypes 1, 4, 5, and 6 when it was combined with 12 weeks of PEG/RBV.

However, the glass ceiling of HCV care was truly shattered with the randomized COSMOS trial, a late-breaker abstract that revealed 12-week functional cure rates in patients receiving sofosbuvir in combination with the protease inhibitor simeprevir.

This phase 2a trial in treatment-naive and -experienced genotype 1 patients with and without cirrhosis showed that an all-oral option was not only viable for the most common strain of HCV but was also safe and efficacious, even in difficult-to-treat populations.

On December 6, 2013, the US Food and Drug Administration (FDA) approved sofosbuvir for the treatment of HCV, ushering in a new era of therapy.

Guidelines quickly changed to advocate for both expansive HCV screening and generous treatment. Yet, as this more permissive approach was being recommended, the high price tag and large anticipated volume of those seeking prescriptions were setting off alarms. The drug cost triggered extensive restrictions based on degree of fibrosis, sobriety, and provider type in an effort to prevent immediate healthcare expenditures.

Given its high cost, rules restricting a patient to only one course of sofosbuvir-based therapy also surfaced. Although treatment with first-generation protease inhibitors carried a hefty price of $161,813.49 per sustained virologic response (SVR), compared with $66,000-$100,000 for 12 weeks of all-oral therapy, its uptake was low and limited by side effects and comorbid conditions. All-oral treatment appeared to have few medical barriers, leading payers to find ways to slow utilization. These restrictions are now gradually being eliminated.

Because of high SVR rates and few contraindications to therapy, most patients who gained access to treatment achieved cure. This included patients who had previously not responded to treatment and prioritized those with more advanced disease.

This quickly led to a significant shift in the population in need of treatment. Prior to 2013, many patients with HCV had advanced disease and did not respond to prior treatment options. After uptake of all-oral therapy, individuals in need were typically treatment naive without advanced disease.

This shift also added new psychosocial dimensions, as many of the newly infected individuals were struggling with active substance abuse. HCV treatment providers needed to change, with increasing recruitment of advanced practice providers, primary care physicians, and addiction medication specialists.

Progress, but Far From Reaching Targets

Fast-forward to 2022.

Nearly 10 years after FDA approval, 13.2 million individuals infected with HCV have been treated globally, 82% with sofosbuvir-based regimens and most in lower- and middle-income countries. This is absolutely cause for celebration, but not complacency.

In 2016, the World Health Assembly adopted a resolution of elimination of viral hepatitis by 2030. The World Health Organization (WHO) defined elimination of HCV as 90% reduction in new cases of infection, 90% diagnosis of those infected, 80% of eligible individuals treated, and 65% reduction of deaths by 2030.

Despite all the success thus far, the CDA Foundation estimates that the WHO elimination targets will not be achieved until after the year 2050. They also note that in 2020 over 50 million individuals were infected with HCV, of which only 20% were diagnosed and 1% annually treated.

The HCV care cascade, by which the patient journeys from screening to cure, is complicated, and a one-size-fits-all solution is not possible. Reflex testing (an automatic transition to HCV polymerase chain reaction [PCR] testing in the lab for those who are HCV antibody positive) has significantly improved diagnosis. However, communicating these results and linking a patient to curative therapy remain significant obstacles.

Though daunting, HCV elimination is not impossible. Although, comparatively, the United States remains behind the curve, the White House has asked Congress for $11 billion to fund HCV elimination domestically.

Models and real-life experience show that multiple strategies can be successful. They include leveraging the electronic medical record, simplified treatment algorithms, test-and-treat strategies (screening high-risk populations with a point-of-care test that allows treatment initiation at the same visit), and co-localizing HCV screening and treatment with addiction services and relinkage programs (finding those who are already diagnosed and linking them to treatment).

In addition, focusing on populations at high risk for HCV infection — such as people who inject drugs, men who have sex with men, and incarcerated individuals — allows for better resource utilization.

Though daunting, HCV elimination is not impossible. There are several examples of success, including in the countries of Georgia and Iceland. Although, comparatively, the United States remains behind the curve, the White House has asked Congress for $11 billion to fund HCV elimination domestically.

As we await action at the national level, clinicians are reminded that there are several things we can do in caring for patients with HCV:

- A one-time HCV screening is recommended in all individuals aged 18 or older, including pregnant people with each pregnancy.
- HCV antibody testing with reflex to PCR should be used as the screening test.
- Pan-genotypic all-oral therapy is recommended for patients with HCV. Cure rates are greater than 95%, and there are few contraindications to treatment.
- Most people are eligible for simplified treatment algorithms that allow minimal on-treatment monitoring.

Without increased screening and linkage to curative therapy, we will not meet the WHO goals for HCV elimination. ■

Dr. Reau is chief of the hepatology section at Rush University Medical Center in Chicago, Illinois, and a regular contributor to this news organization. She serves as editor of Clinical Liver Disease, a multimedia review journal, and recently as a member of HCVGuidelines.org, a web-based resource from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America, as well as educational chair of the AASLD hepatitis C special interest group. She continues to have an active role in the hepatology interest group of the World Gastroenterology Organisation and the American Liver Foundation at the regional and national levels. She disclosed ties with AbbVie, Gilead, Arbutus, Intercept, and Salix.

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