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Important questions remain over UnitedHealthcare's advance notification program, according to the AGA.

UHC offers little guidance on advance notification

BY AMY REYES
MDedge News

It's been just over 2 months since UnitedHealthcare (UHC) launched its advance notification program on June 1 requiring providers to record nonscreening colonoscopy and other gastroenterology procedures to be eligible for its 2024 Gold Card program.

The program, which will begin next year, may eliminate prior authorization requirements for providers who successfully complete the advance notification program this year. However, there is no guarantee that providers who complete the advance notification program will be enrolled in the Gold Card program, which means they would have to seek prior authorization for nonscreening procedures, says the American Gastroenterological Association.

While UHC has provided some information about how advance notification works, there are unanswered questions, said Barbara H. Jung, MD, AGAF, AGA president.

See **UHC** · *page 8*

Mirikizumab performs well in UC, new data show

BY THOMAS R. COLLINS
MDedge News

The interleukin-23 (IL-23) inhibitor mirikizumab performed better than placebo for ulcerative colitis with patients showing good results on histological testing and control of bowel movements, according to new findings from the phase 3 LUCENT-1 induction and LUCENT-2 maintenance trials. The findings were reported in the New England Journal of Medicine (2023;388:2444-55).

Mirikizumab manufacturer Eli Lilly, which funded the study, is hoping the drug will become the first IL-23 inhibitor to be approved in the United States for ulcerative colitis. The drug targets the p19 subunit that is unique to IL-23. Ustekinumab, which targets the p40 subunit that is shared by IL-12 and IL-23, has been approved for UC and Crohn's disease. Risankizumab, which targets the IL-23 p19 subunit, has been approved for Crohn's treatment.

Earlier this year, the Food and Drug Administration rejected Lilly's mirikizumab application over manufacturing issues, with no concerns about the clinical data, safety, or labelling. The company said it was working with the FDA to resolve the concerns, and hopes

See **Mirikizumab** · *page 8*

Mucosal exposure device boosts AI-assisted detection of adenomas

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

Performing colonoscopy with a mucosal exposure device and artificial intelligence (AI) software increases detection of adenomas over AI-assisted colonoscopy alone, based on results of a randomized trial.

Using the mucosal exposure device increased adenoma detection rate by 12% without impacting safety or withdrawal time, suggesting that the two approaches have a synergistic

See **AI** · *page 9*

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LETTER FROM THE EDITOR

Ensuring trustworthy health AI

At DDW in May, the AGA Ethics Committee sponsored a well-attended clinical symposium focused on key legal, regulatory, and ethical considerations relating to use of artificial intelligence (AI) in health care.

It was a thought-provoking discussion of how to ethically and equitably design and regulate these exciting new technologies to maximize their potential to achieve meaningful improvements in health for our patients while avoiding unintended consequences.

Dr. Adams

Indeed, one of the vexing challenges in this space is the fact that many AI algorithms and resulting tools are proprietary, impeding the ability to achieve the level of transparency necessary to understand data inputs, outputs, and outcomes, and assess for potential algorithmic bias.

This is an area that remains largely unregulated, with a lack of common standards to guide responsible design, development, and adoption of these tools. This is something that is top of mind for federal regulatory agencies, including the Food and Drug Administration, which in September 2022, announced plans to expand its regulation of AI-powered clinical decision support tools as medical devices.

There are also attempts underway to harmonize standards and reporting for health AI and educate end-users on how to evaluate these technologies to drive their responsible adoption. For example, the Coalition for Health AI, a community of academic health systems, organizations, and expert practitioners of AI and data science, recently released its Blueprint for Trustworthy AI Implementation Guidance and Assurance for Healthcare in April 2023. This is a topic we will surely hear more about in the coming years, and one I encourage you to read about in greater depth as it is truly eye-opening.

In this month's issue of GI & Hepatology News, we update you on a new fatty liver disease nomenclature (including several new acronyms) that will be critical to incorporate into your clinical practice moving forward. In a new recurring article reprinted from Gastro Hep Advances, we highlight important Pearls from the Pros from hepatologists Dr. Lawrence Friedman and Dr. Paul Martin on the management of incidental hepatic steatosis. Our August Member Spotlight features Orlando-based gastroenterologist Dr. Mariam Naveed, who shares her passion for medical education and experience starting a new GI fellowship program.

We hope you enjoy these and all the stories featured in our August issue.

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

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 careers. AGA's flagship award is the Research Scholar Award (RSA), which provides career development support for young investigators in gastroenterology and hepatology research.

The AGA Research Awards program has had a significant impact on digestive disease research.

- More than $58 million has been awarded in research grants.
- More than 1,000 scientists have been awarded grants.
- 57% of RSA recipients subsequently received at least one NIH R01 award, with 5 years on average between the RSA and first R01. Investigators received 280 R01 or equivalent awards.

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

"In order to produce truly innovative work at the forefront of current discoveries, donations to research in GI are essential and cannot be replaced by other funding sources," states Kathleen Curtius, PhD, MS, 2022 AGA Foundation Research Scholar Award recipient.

Join others in supporting the AGA Research Foundation. Your tax-deductible contribution supports the Foundation's research award program, including the RSA, which ensures that studies are funded, discoveries are made, and patients are treated.

To learn more or to make a contribution, visit www.foundation.gastro.org. ■

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Member SPOTLIGHT

Florida GI gets candid about imposter syndrome, insurers, developing a GI fellowship

BY JENNIFER LUBELL
MDedge News

Looking back on her career as a gastroenterologist, Mariam Naveed, MD, sees the gastroenterology fellowship program she created at AdventHealth in Orlando as a pinnacle moment.

Her first faculty position as assistant program director for the gastroenterology fellowship program at the University of Iowa offered some inspiration. "I loved teaching and working with trainees and knew I always wanted to remain in this realm," Dr. Naveed said.

When she moved to Orlando to join AdventHealth, she noticed there was no gastroenterology training program. "I was strictly in private practice. Though I love working with patients, I constantly felt like something was missing. When the opportunity to start a fellowship program came, I was highly motivated to bring it to fruition."

The AdventHealth fellowship is almost done with its inaugural year.

"Starting a fellowship at a new institution is a very challenging yet incredibly rewarding experience," she said.

In this Q&A, she discusses her strategies for dealing with insurance companies and imposter syndrome, and why she looks to her father as her role model in medicine.

Q: Why did you choose GI?
Dr. Naveed: Gastroenterology is a rapidly evolving field which makes it incredibly fascinating. The initial draw was that I was always excited to learn about GI physiology and disease. I also was fortunate to train with amazing gastroenterologists during residency. I had great examples of strong and successful female GIs to look up to. Lastly, for the most part, gastroenterologists are all fairly laid back and have an interesting sense of humor.

Q: What gives you the most joy in your day-to-day practice?
Dr. Naveed: I love learning and teaching. As a program director, I am directly involved with fellows, residents, and students, but there are always additional enrichment opportunities beyond these interactions. I value teaching clinic medical assistants so they feel more confident and empowered in their work. I also try to educate my nurse practitioners. The best compliment at the end of a long day is that they learned something valuable.

Q: How do you stay current with advances in your field?
Dr. Naveed: Between my role as a physician and as an educator, I owe it to my patients and trainees to stay current with advances in the field. But of course, this is challenging, and at times it feels like there are not enough hours in the day. While reading journal articles and attending conferences are great ways to refresh one's knowledge, the winner for me has been social media (specifically Twitter). It's easy to find a "Tweetorial" on almost any topic. There are some excellent initiatives on Twitter such as Monday Night IBD, ACG Evidence-Based GI Doc, Scoping Sundays, and GI Journal Club where important articles, new treatment options, and challenging cases are discussed. Of course, I also learn a lot from my fellows and residents.


Dr. Mariam Naveed

Q: What fears did you have to push past to get to where you are in your career?
Dr. Naveed: Pushing past imposter syndrome, which is a feeling of self-doubt despite education, experience, and accomplishments. It is something many of us deal with. I've had to retire the notion that I am not experienced enough to achieve a particular career goal.

Q: What habits have you established that have benefited your career most?
Dr. Naveed: It's a challenge to not immediately say "yes" to every opportunity or project. It's also difficult to learn to delegate. I am lucky to have a great team, and I have learned that delegating certain tasks or projects helps everyone grow. Also, if I say no to an opportunity, I still try to suggest another colleague or mentee who may be interested and/or a good fit.

Q: Describe your biggest practice-related challenge and what you are doing to address it.
Dr. Naveed: Pushback from insurance companies to approve medications or interventions is incredibly frustrating for myself and the patient. It is also incredibly time consuming and requires significant clinical bandwidth that could otherwise be used in other capacities. While not a solution, I at least try to make sure the patient is kept updated and understands causes of delay, and more importantly, what we are doing to address the issue. I have realized that it's always preferable to empower the patient, rather than leave them uninformed, which can foster frustration and dissatisfaction.

Q: What teacher or mentor had the greatest impact on you?
Dr. Naveed: I have been blessed with many mentors at different points in my medical career that have greatly impacted and shaped my journey. During my fellowship at University of Texas Southwestern (UTSW), Nisa Kubiliun, MD, was not only a mentor, but also an incredible sponsor. She saw potential in me and encouraged involvement in activities critical for career advancement. Arjmand Mufti, MD, the former program director of the UTSW GI fellowship, is still always just a call away when I need advice regarding my GI fellowship program at AdventHealth. I also have mentors and sponsors within my own institution who invest time and energy into my success.

Q: Outside of teachers and mentors, who or what has had the strongest influence in your life?
Dr. Naveed: My father, who is also a physician, has had a profound influence on my personal and professional development. His own medical journey has been incredibly unique. He has practiced medicine internationally, trained and worked in a traditional academic setting, established a very successful private practice, and now has transitioned to running a hospital-based practice. He has seen it all (and he's also a brilliant physician), and he is always able to talk me through any situation.

Q: What principles guide you?
Dr. Naveed: Treating my patients how I would want a physician to treat my family is central to my practice. Also, I try to approach any successes with gratitude, and likewise, be patient with inevitable failures. It can be challenging, but I try to find the lesson in every failed venture.

Q: What would you do differently if you had a chance?

Continued on following page

Lightning round

If you weren't a gastroenterologist, what would you be?
International event planner

How many cups of coffee do you drink a day?
Usually three

What's your favorite breakfast?
Eggs, corned beef hash, toast

Do you prefer talking or texting?
Texting, unless it's Mom or Dad who always get a call.

Where do you most want to travel?
Japan

Liver disease gets new name and diagnostic criteria

BY JENNIE SMITH
MDedge News

Nonalcoholic fatty liver disease will now be called metabolic dysfunction–associated steatotic liver disease, or MASLD, according to new nomenclature adopted by a global consensus panel composed mostly of hepatology researchers and clinicians.

The new nomenclature, published in the journal Hepatology (2023 Jun 24. doi: 10.1097/HEP.0000000000000520), includes the umbrella term steatotic liver disease, or SLD, which will cover MASLD and MetALD, a term describing people with MASLD who consume more than 140 grams of alcohol per week for women and 210 grams per week for men.

Metabolic dysfunction–associated steatohepatitis, or MASH, will replace the term nonalcoholic steatohepatitis, or NASH.

Mary E. Rinella, MD, of University of Chicago Medicine led the consensus group. The changes were needed, Dr. Rinella and her colleagues argued, because the terms "fatty liver disease" "and nonalcoholic" could be considered to confer stigma, and to better reflect the metabolic dysfunction occurring in the disease. Under the new nomenclature, people with MASLD must have a cardiometabolic risk factor, such as type 2 diabetes. People without metabolic parameters and no known cause will be classed as having cryptogenic SLD.

While the new nomenclature largely conserves existing disease definitions, it allows for alcohol consumption beyond current parameters for nonalcoholic forms of the disease. "There are individuals with risk factors for NAFLD, such as type 2 diabetes, who consume more alcohol than the relatively strict thresholds used to define the nonalcoholic nature of the disease [and] are excluded from trials and consideration for treatments," the authors wrote.

Moreover, they wrote, "within MetALD there is a continuum where conceptually the condition can be seen to be MASLD or ALD predominant. This may vary over time within a given individual."

Respondents overwhelmingly agreed, however, that even moderate alcohol use alters the natural history of the disease and that patients with more than minimal alcohol consumption should be analyzed separately in clinical trials.

The new nomenclature reflects a 3-year effort involving some 236 panelists from 56 countries who participated in several rounds of online surveys using a Delphi process. Pediatricians, gastroenterologists, and endocrinologists also participated as well as some patient advocates. Changes were based on a super-majority of opinion (67% or higher), though the consensus on whether the term "fatty" was stigmatizing never reached that threshold. In early rounds of surveys only 44% of respondents considered the word "fatty" to be stigmatizing, while more considered "nonalcoholic" to be problematic.

The new nomenclature includes the umbrella term steatotic liver disease, or SLD, which will cover MASLD and MetALD for women who consume more than 140 grams of alcohol weekly, and men who drink more than 210 grams weekly.

"Substantial proportions of the respondents deemed terms such as 'fatty' stigmatizing, hence its exclusion as part of any new name," Dr. Rinella and her colleagues wrote. "Although health care professionals may contend that patients have not reported this previously, this likely reflects in part a failure to ask the question in the first place and the power imbalance in the doctor-patient relationship." The authors noted that the new terminology may help raise awareness at a time when new therapeutics are in sight and it becomes more important to identify at-risk individuals.

Of concern was whether the new definitions would alter the utility of earlier data from registries and trials. However, the authors determined that some 98% of people registered in a European NAFLD cohort would meet the new criteria for MASLD. "Maintenance of the term, and clinical definition, of steatohepatitis ensures retention and validity of prior data from clinical trials and biomarker discovery studies of patients with NASH to be generalizable to individuals classified as MASLD or MASH under the new nomenclature, without impeding the efficiency of research," they stated.

The effort was spearheaded by three international liver societies: La Asociación Latinoamericana para el Estudio del Hígado, the American Association for the Study of Liver Diseases, and the European Association for the Study of the Liver, as well as the cochairs of the NAFLD Nomenclature Initiative.

Each of the authors disclosed a number of potential conflicts of interest. ■

Continued from previous page

Dr. Naveed: I have always had an interest in international medical missions but have yet to participate in one. I have previously passed on such opportunities, thinking it was not the right time, but in hindsight I wish I had taken the leap. I still hope to eventually accomplish this goal.

Q: Describe a scene of your vision for the future.
Dr. Naveed: I hope that our GI fellowship continues to flourish and attract exceptional faculty and candidates. I want to remain involved in graduate medical education, but I hope to continue to challenge myself and advance within this domain. Most importantly, I hope I can continue to balance my career aspirations with my personal goals. I want to continue to be present for my family and kids.

Q: Describe how you would spend a free Saturday afternoon.
Dr. Naveed: You can usually find me at the local farmer's market with my husband and kids. Afterwards, we're definitely going to get Chick-fil-A followed by ice cream. ■

Follow Dr. Naveed on Twitter at @MN_GIMD

Questions remain about UHC's new policies

UHC *from page 1*

"UnitedHealthcare's haphazard approach to rolling out a policy that will ultimately control patient access to critical, often lifesaving medical procedures is the opposite of what should be our common goal of expeditious access to essential care," she said.

The advance notification program was announced on June 1 when UHC said it was dropping its controversial prior authorization program, which was due to go into effect that day.

Dr. Jung

AGA is concerned that UHC's advance notification program is merely a delay tactic because prior authorization may be required next year for providers who are not accepted into the Gold Card program. Providers who are not accepted into the program may face delays in administering procedures due to the need for prior authorizations. Thousands of endoscopies and colonoscopies could potentially be disrupted in the first month alone due to canceled procedures because of new prior authorization requirements, they said.

UHC has been trying to rein in health care costs by first considering prior authorization for most gastrointestinal endoscopic procedures, except for screening colonoscopy, but ultimately adopting advance notification. Providers, UHC has said, don't always follow evidence-based medicine treatment recommendations or they overutilize procedures. UHC's goal is "better care, improved health outcomes, and lower costs," the company stated.

"Clinical studies demonstrate overutilization of these procedures and lack of adherence to specialty society–endorsed guidelines and recommendations. Up to one-third of upper GI procedures and almost half of nonscreening colonoscopies performed for common clinical conditions are not consistent with clinical guidelines," UHC stated in an FAQ. However, according to a statement from the AGA, it has not seen utilization data specific to UHC: "It is clear that UHC does not currently have any data indicating significant overutilization of critical colonoscopy and endoscopy procedures and therefore [there is] no justification to impose burdensome barriers like prior authorization."

AGA also pointed to research showing there is an unmet need for colonoscopies in the United States, which suggests there is underutilization of this crucial procedure (Cancer. 2023 May 1;129[9]:1394-401).

The advance notification policy comes despite immense pressure from physicians, patients, lawmakers, and regulators to crack down on prior authorization policies. "AGA has expressed our willingness to work collaboratively with UnitedHealthcare to address any concerns and educate physicians, but communication and transparency with the insurer are nearly nonexistent. Instead, the GI community is confronted with a nebulous concept called advance notification, which is not conducive to seamless patient care. Ultimately, it appears advance notification will form the basis of prior authorization, which we know can delay, disrupt, and deny timely care," Dr. Jung said.

How advance notification works

Effective June 1, providers have been asked to provide advance notification for nonscreening GI endoscopy procedures that include: esophagogastroduodenoscopy, capsule endoscopy, diagnostic colonoscopy, and surveillance colonoscopy. The notification can be made by phone (866-889-8054) or through a UHC online portal at UHCprovider.com.

Advance notification applies to patients who have UHC commercial plans, including UnitedHealthcare, UnitedHealthcare Plan of the River Valley, Neighborhood Health Partnership, UnitedHealthcare Level Funded, and UnitedHealthcare Oxford Health Plans in all states, except Rhode Island, Kentucky, and New Mexico.

Providers who opt out of participating in advance notification will not be eligible to participate in the Gold Card program in 2024. This program will essentially allow providers to order most GI endoscopy procedures, except for screening colonoscopy, without prior authorization. However, UHC has not released information about how it will implement its planned Gold Card prior authorization program or how many providers will be accepted into the program.

UHC has assured providers it will not issue medical necessity denials through this process, but it may ask providers to participate in a "comprehensive peer-to-peer discussion with a board-certified gastroenterologist around clinical guidelines."

The fear for practices is that advance notification will be an onerous process adding burdensome paperwork that practices are not equipped to manage. UHC is the largest health insurer in the country representing 46% of the total market.

Lawrence Kim, MD, AGAF, vice president of AGA and a gastroenterologist practicing in Denver said that each physician in his practice does over 1,000 procedures annually and 25% of their patients carry UHC.

"We are currently completing 30-40 notifications a day, requiring two staff members to comply with this program. UHC is not asking for any clinical information, just procedure and diagnosis codes, and in some cases site of service. The advance notification program as it stands will not provide UHC with additional information beyond what they already have through claims data. This highlights the strain these requirements are putting on providers and practices for repetitive data," he said.

For more information, visit UHC at shorturl.at/gFNZ2. To learn more about AGA's advocacy, visit www.gastro.org/UHC. ■

IL inhibitor market grows 5-fold

Mirikizumab *from page 1*

to "launch mirikizumab in the U.S. as soon as possible." The drug has already been approved in Japan for moderately and severely active ulcerative colitis, and the drug was reviewed favorably by the European Medicines Agency.

Since 2014, the market size of interleukin inhibitors has grown fivefold with the greatest share belonging to IL-23 inhibitors.

The induction trial included 1,281 patients with moderately or severely active ulcerative colitis (UC), and 544 patients who had a response to mirikizumab were randomized again in the maintenance phase.

Significantly more patients in the mirikizumab arm – 24.1% ($P < .001$) – had clinical remission at week 12, although there was a high placebo remission rate, as is often seen in UC trials, at 13.3%. At week 40 of the maintenance trial, 49.9% of those on mirikizumab had clinical remission, compared to 25.1% for placebo ($P < .001$).

Mirikizumab also performed better than placebo on the trial's five secondary endpoints: glucocorticoid-free clinical remission (44.9% to 21.8%), maintenance of clinical remission (63.6% to 36.9%), endoscopic remission (58.6% to 29.1%), histologic-endoscopic mucosal remission (43.3 %), and bowel-urgency remission (42.9% to 25.0%) ($P < .001$ for all).

Researchers led by Geert D'Haens, MD, PhD, professor of gastroenterology at Amsterdam University Medical Centers, emphasized the effects on acute inflammatory cell infiltration.

"Current recommendations for the treatment of ulcerative colitis include increasingly rigorous goals beyond symptomatic or endoscopic improvement. Recent literature has recommended the absence of intraepithelial neutrophils as a minimal requirement for remission on the basis of histologic testing," authors wrote.

Urgency NRS (Numeric Rating Scale) – a measure developed by Lilly in which patients report the urgency of bowel movements over the previous 24 hours – was used in the trial.

"Many patients with ulcerative colitis consider control of bowel movements to be more important than rectal bleeding or stool frequency. In the induction trial, patients reported reductions in bowel urgency with mirikizumab therapy, which were sustained during the maintenance trial," researchers said.

Of the 1,217 patients treated with mirikizumab during the placebo-controlled and non–placebo-controlled periods, opportunistic infections were seen in 15, with 6 herpes zoster infections. One case of an opportunistic infection was seen in a patient receiving placebo in the induction trial.

The authors disclosed consultancies, or other relationships, with a number of pharmaceutical companies, including Eli Lilly. ■

Naltrexone is safe, beneficial in AUD with cirrhosis

BY BECKY MCCALL

VIENNA – Naltrexone can be safely administered to patients with alcohol use disorder (AUD) and compensated cirrhosis to help them achieve abstinence and decrease craving, results of the first randomized controlled trial (RCT) show.

After 3 months, 64% of patients who received naltrexone were abstinent from alcohol, compared with 22% of patients who received placebo, Manasa Alla, MD, a hepatologist from the Institute of Liver and Biliary Sciences (ILBS), New Delhi, said at the European Association for the Study of the Liver (EASL) 2023, where she presented the study findings.

Importantly, naltrexone was found to be safe for patients with compensated cirrhosis.

"This fragile population of patients has limited drugs to help them quit alcohol. Naltrexone can be a valuable addition to their measures to reduce craving and on their journey to reach de-addiction and abstinence," Dr. Alla said.

Hepatotoxicity with naltrexone is rare and data are limited. The Food and Drug Administration previously placed a warning on its use for patients with alcoholic liver disease and underlying cirrhosis.

As a clinician constantly challenged with treating patients with AUD and cirrhosis, Dr. Alla wanted to explore the safety of naltrexone and to test its suitability for these patients who struggle to quit alcohol.

"Here we aimed to primarily test the safety of naltrexone in achieving abstinence and reducing alcohol cravings in patients with alcohol-related cirrhosis," she said, adding, "The FDA black box warning has been removed, but it has never been tested in an RCT in patients with cirrhosis, so this is exactly what we did here. Naltrexone is a very good anti-alcohol craving drug. If we can establish its safety in

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ZzVuk/E+/Getty Images

CADe/ECV-assisted colonoscopy

AI *from page 1*

effect, wrote study authors who were led by Marco Spadaccini, MD, Humanitas University, Pieve Emanuele, Italy.

"Recent advances in AI, deep learning, and computer vision led to implementation of computer-aided detection [CADe] of colorectal polyps," the investigators wrote in Gastroenterology (2023 Apr 13. doi: 10.1053/j.gastro.2023.03.237). "CADe-assisted colonoscopy already proved its efficacy by increasing adenoma detection in randomized parallel and crossover trials. However, such benefit is mostly related to the higher accuracy in spotting lesions already within the visual field, not affecting the amount of mucosa exposed by the endoscopist during the scope withdrawal. Increasing the mucosa exposure represents a complementary strategy to CADe in order to further improve detection of colorectal neoplasia."

To test their hypothesis, the investigators conducted a randomized trial involving 1,316 subjects undergoing routine colonoscopy at six centers in Italy and Switzerland. Participants were randomized in a 1:1 ratio to undergo colonoscopy with CADe (GI Genius, Medtronic) or CADe plus a mucosal exposure device (Endocuff Vision, Olympus).

The combination approach yielded a 49.6% adenoma detection rate, compared with a 44.0% detection rate for CADe alone (relative risk, 1.12; 95% confidence interval, 1.00-1.26; $P = .04$). Adding the mucosal exposure device was also associated with a higher number of adenomas detected per colonoscopy. Withdrawal time and rate of unnecessary polypectomies did not differ between groups.

"The benefit of adding [the mucosal exposure device] to AI was expected due to the complementary nature of the interventions," Dr. Spadaccini and colleagues wrote. "The benefit of [the mucosal exposure device] is limited to increase the quantity of mucosa exposed to the lens by flatting the folds and strengthening the angulations, and the benefit of AI is only in spotting a lesion that is already displayed within the field of view. Thus, we may speculate that the additional mucosal exposure was synergistic to the AI-assisted polyp recognition by AI."

The benefits of a combination approach were not universal, however, as the mucosal exposure device did not improve detection of either serrated lesions or advanced adenomas. This result was anticipated since the miss rate for diminutive or proximal adenomas is higher than it is for larger or distal lesions, and previous research has suggested that AI-assisted and mucosal exposure techniques, when used alone, are most effective for detecting smaller, proximal lesions, investigators wrote.

The study was funded by a European Society of Gastrointestinal Endoscopy Artificial Intelligence Award. The investigators disclosed additional relationships with Fujifilm, Medtronic, Olympus, and others. ■

The paradigm of adenoma detection is rapidly shifting within the context of screening-related colonoscopy. If one considers the various interventions available to improve one's adenoma detection rate (ADR), the landscape is vastly different than it was 5-10 years ago. Two established interventions with robust supporting data from randomized controlled trials (RCTs) are computer-aided detection (CADe) platforms such as GI Genius (Medtronic) and distal attachment devices such as Endocuff Vision (Olympus). This RCT by Spadaccini and colleagues tested the intuitive hypothesis that these interventions applied together boost ADR, compared with CADe alone.

Dr. Forbes

In a patient cohort that was balanced across major colonoscopy indications of primary screening, positive fecal immunochemical testing, surveillance, and diagnosis, ADR was 12% higher in patients receiving colonoscopy with Endocuff Vision and CADe, compared with CADe alone, with a corresponding significant increase in the adenoma per colonoscopy rate of 26%. Detection of advanced adenomas was not significantly different between groups. Detection of serrated lesions was also similar.

Real-world studies of CADe's effectiveness on ADR are less impressive than efficacy data from trials. Whereas CADe platforms require a significant one-time investment, distal attachment devices represent a small fraction of single procedural costs which then incrementally add up when used over large volumes. More head-to-head studies, cost-effectiveness analyses, and real-world studies are needed to elucidate the best single and/or combination strategies for optimizing ADR. In the meantime, endoscopists should be aware of all evidence-based techniques for ADR improvement, including those that can be incorporated at little to no cost.

Nauzer Forbes, MD, MSc, FASGE, is an associate professor at the University of Calgary (Alta.), where he is the training program director for advanced/therapeutic endoscopy. He is a consultant for and has received speaker's fees from Pentax Medical and Boston Scientific, is a consultant for AstraZeneca, and has received research funding from Pentax Medical.

Continued from previous page

cirrhotic patients, it may have very good potential in reducing AUD and reducing the related complications of continued alcohol intake," Dr. Alla said.

Safety, abstinence, lapse, and relapse assessed

The prospective, double-blind, single-center study at the ILBS in New Delhi, enrolled 100 patients with alcohol dependence and cirrhosis between 2020 and 2022. Participants were randomly assigned in a 1:1 ratio to receive naltrexone (50 mg/d) or placebo for 12 weeks. All participants attended regular counseling sessions with the resident psychiatrist. At baseline, the biochemical and drinking-related assessment

"Any intervention that can reduce or stop alcohol use in patients with cirrhosis and more advanced cirrhosis will improve outcome as well as reduce complications and mortality," Dr. Aleksander Krag said.

scores between active and placebo groups of patients with compensated cirrhosis were matched.

Abstinence from alcohol was assessed through self-reported mean number of standard drinks (12 g alcohol per day). Findings were corroborated through an interview with a family member. Serum ethyl glucuronide levels were measured in cases of discrepancy. A relapse was considered to be consumption of over four standard alcoholic drinks/month; a lapse was considered any other alcohol drinking event not classified as relapse.

The primary outcome was the proportion of patients who achieved and maintained alcohol abstinence at 12 weeks; secondary outcomes were the proportion of patients who took naltrexone without a liver-related adverse effect compared with placebo at 12 weeks, the number of relapses and lapses, the difference in craving scores on the Obsessive Compulsive Drinking Scale (OCDS) between groups at 4, 8, and 12 weeks and at 6 months and 12 months, and the proportion of patients who achieved and maintained alcohol abstinence at 6 months.

Abstinence at 3 months

After 3 months, abstinence was noted in 64% of the study population who received naltrexone, compared to 22% of those who received placebo ($P < .001$). At 6 months, a higher proportion of patients in the naltrexone group achieved abstinence (22% vs. 8% with placebo; $P = .09$).

"We still need to look at the longer-term effects of naltrexone," Dr. Alla said. "Here we gave the drug plus counseling for 3 months only, so despite encouraging findings, we need further studies to understand more."

The researchers analyzed the predictors of abstinence at 3 months. They found that patients who consumed fewer than 17 drinks per month at baseline were more likely to achieve abstinence (sensitivity, 81%).

"Our study showed that patients who are consuming less alcohol at baseline can quit alcohol if adequately motivated. We need the motivation, as well as the drug," she said.

Patient counseling was also very important and was provided for the 3 months of the study. "Even in the placebo arm, we had some patients who became abstinent [11/50 patients], but this dropped at 6 months [to 4/50]," Dr. Alla said.

At 12 weeks, 28% in the naltrexone group experienced relapse, vs. 72% in the placebo group ($P < .001$). Regarding the secondary outcome of craving scores and how they were affected by naltrexone, the mean OCDS-O (obsessive element) scores were 6.63, compared with 9.29 in naltrexone and placebo, respectively ($P < .01$). The mean OCDS-C (compulsive element) scores were 6.34 and 9.02, respectively ($P < .01$).

"Most important, was the safety of naltrexone in this study," she said. There were no significant adverse events in either arm, and only one patient discontinued the drug in the naltrexone arm. Three patients in the naltrexone group who continued alcohol consumption developed jaundice, "so the jaundice can be attributed to continuous alcohol intake and may not be secondary to the naltrexone per se. We concluded that naltrexone is safe in a compensated cirrhotic patient," Dr. Alla said.

Regarding other adverse events, 13.7% of patients experienced gastritis with naltrexone, vs. 3.7% among patients who received placebo. Nausea was more common in the placebo group, at 11.1% compared with 6.8% among patients who received naltrexone. Vomiting was more common in the naltrexone arm, at 10.3% vs. 7.4% with placebo. None of these differences reached statistical significance.

"Most important, was the safety of naltrexone in this study," Dr. Alla said. There were no significant adverse events in either arm, and only one patient discontinued the drug in the naltrexone arm.

A longer-term study and comparisons to other drugs would provide valuable insights going forward.

Moderator Aleksander Krag, MD, professor and head of hepatology at the University of Southern Denmark and Odense University Hospital in Denmark, said: "Any intervention that can reduce or stop alcohol use in patients with cirrhosis and more advanced cirrhosis will improve outcome as well as reduce complications and mortality.

"In some cases, alcohol rehabilitation can completely revert the damaged liver. We have lots of data that show that continuous alcohol use at the more advanced stages can be devastating and reduction [in alcohol use] improves outcome. Therefore, any intervention that can help us to achieve this on behalf of all patients is most welcome," he said.

Naltrexone (ADDTREX) and identical placebos were supplied by Rusan Pharma. Dr. Alla has disclosed no relevant financial relationships. Dr. Krag has served as speaker for Norgine, Siemens, and Nordic Bioscience and has participated in advisory boards for Norgine and Siemens outside the submitted work. He receives royalties from Gyldendal and Echosens. ■

Biologics, thiopurines, or methotrexate use doesn't affect fertility or birth outcomes in men with IBD

BY THOMAS R. COLLINS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Medications taken by prospective fathers for inflammatory bowel disease (IBD) do not seem to affect fertility or birth outcomes, according to a systematic review and meta-analysis published in Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2022.07.008).

This is the first meta-analysis to assess semen parameters and the risk of adverse outcomes in pregnancy for male patients with IBD who have taken biologics, thiopurines or methotrexate for IBD, researchers said.

"We provide encouraging evidence that biologic, thiopurine, and methotrexate therapy among male patients with IBD, are not associated with impairments in male fertility or with increased risk of adverse pregnancy outcomes," said researchers who were led by John Gubatan, MD, instructor in medicine at Stanford (Calif.) University, who worked with investigators in Copenhagen and Toronto. "Taken together, our data support the safety of continuing biologics, thiopurines, or methotrexate across the reproductive spectrum."

Questions of fertility and pregnancy outcomes are of particular importance in IBD, since patients are often diagnosed around the time of their reproductive years – about 30 years old for Crohn's disease and 35 years old for ulcerative colitis. There has been far more research attention paid to female than male reproductive considerations, mainly the health of the fetus when the mother takes biologic therapy for IBD during pregnancy, which has generally found to be safe.

Researchers found no differences between sperm count, motility, or morphology between those exposed and not exposed to biologics, thiopurines, and methotrexate, with a couple of exceptions.

Their search found 13 studies with male IBD patients exposed to biologics, 10 exposed to thiopurines, and 6 to methotrexate. Researchers extracted data on sperm count, sperm motility, and abnormal sperm morphology – three metrics considered a proxy for male fertility – as well as early pregnancy loss, preterm birth, and congenital malformations.

Researchers found no differences between sperm count, motility, or morphology between those exposed and not exposed to biologics, thiopurines, and methotrexate, with a couple of exceptions. They actually found that sperm count was higher for thiopurine users, compared with nonusers, and there was only one study on methotrexate and abnormal sperm morphology, so there was no data to pool together for that comparison.

In a subgroup analysis, there was a trend toward higher sperm count in thiopurine users, compared with biologic or methotrexate users, but no differences were seen in the other parameters.

Similarly, there were no significant differences for users and nonusers of these medications for early pregnancy loss, preterm births, or congenital malformations, the researchers found.

A prior systematic review suggested that azathioprine might be associated with low sperm count, but this new analysis calls that into question.

"Our results, which demonstrated that thiopurine use among male patients with IBD is associated with increased sperm count, refute this prior finding," the researchers said. The previous finding, they noted,

There were no significant differences for users and nonusers of these medications for early pregnancy loss, preterm births, or congenital malformations.

was only qualitative because the authors didn't do an analysis to calculate effect size or determine statistical significance.

"Furthermore," the researchers said, "our study included more updated studies and a greater number of patients."

The authors disclosed no conflicts of interest. ■

BOJANSTORY/GETTY IMAGES

IBD treatment agents were not associated with fertility issues in men, a study shows.

Understanding the impact of inflammatory bowel disease therapies on fertility and pregnancy outcomes is key toward managing patients with IBD. While there is substantial research on the implications of maternal exposure to IBD medications with reassuring safety data, research in the context of paternal exposure to IBD medications is limited.

Dr. Agrawal

In this systematic review and meta-analysis, Gubatan and colleagues explore the impact of IBD medications on male fertility and pregnancy outcomes. They report that exposure to biologics (predominantly anti–tumor necrosis factor agents), thiopurines, and methotrexate was not associated with a negative impact on sperm count, sperm motility, sperm morphology, early pregnancy loss, premature birth, or congenital malformations. However, analyses of outcomes with vedolizumab, ustekinumab, and methotrexate were limited by small numbers.

This study represents the largest report summarizing data across diverse populations on the topic with reassuring results. It carries important implications in clinical practice and provides further evidence in support of continuing IBD therapy among male patients through pregnancy planning. Certainly, active IBD in male patients is associated with adverse effects on sperm quality and conception likelihood, and it is important to achieve remission prior to pregnancy planning.

Further research on the impact of paternal exposure to newer biologics, including small molecule drugs, and additional analyses after adjusting for potential confounders will advance the field and provide further guidance in clinical practice.

Manasi Agrawal, MD, MS, is an assistant professor of medicine in the Dr. Henry D. Janowitz Division of Gastroenterology at the Icahn School of Medicine at Mount Sinai, New York. She is a research associate with the Center for Molecular Prediction of Inflammatory Bowel Disease. Aalborg University, Copenhagen. She reports no conflicts.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Race and ethnicity loom large in CRC screening

BY JENNIE SMITH
MDedge News

TECHNIQUES AND INNOVATIONS IN GASTROINTESTINAL ENDOSCOPY

While increases in colorectal cancer screening have been linked to drops in disease incidence, marginalized racial and ethnic populations in the United States continue to see lower screening rates along with higher disease incidence and mortality. Disparities in colorectal screening represent a serious public health challenge, say the authors of a new literature review that describes specific areas of concern and recommendations for improvement.

The study authors pointed to structural racism at the root of some observed disparities, citing barriers to health care access.

Published in Techniques and Innovations in Gastrointestinal Endoscopy (2023 Feb 28. doi: 10.1016/j.tige.2023.02.007), gastroenterologists Abraham Segura, MD, and Shazia Mehmood Siddique, MD, of the University of Pennsylvania, Philadelphia, sought to identify studies that shed light on ethnicity or race-based differences in screening uptake, as well as known barriers to screening.

Significant racial and ethnic disparities can be seen in rates of colonoscopy selection as a screening method, and of screening completion, Dr. Segura and Dr. Siddique noted, with White individuals who chose the method three times more likely to complete screening as Asian, Hispanic, or Black individuals. Disparities were also seen reflected in people's choice of screening method, with non–English-speaking Hispanic individuals less likely to choose colonoscopy compared with other groups.

Use of stool-based screening methods, such as the fecal occult blood test (FOBT) and fecal immunochemical test (FIT), has risen over time across ethnic and racial groups. However, Hispanic and Asian individuals were more likely to complete and adhere to the FOBT, compared with non-Hispanic White individuals. Follow-up colonoscopy rates after FOBT or FIT also differ along ethnic and racial lines with Asian and American Indian groups less likely to complete follow-up after an abnormal result.

The study authors pointed to structural racism at the root of some observed disparities, citing barriers to health care access and quality that include higher rates of noninsurance

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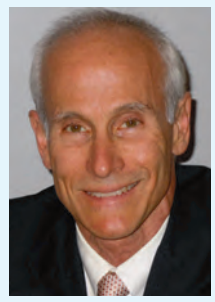
Understanding disparities in medicine is the requisite first step toward achieving health equity. The review by Segura and Siddique highlight reasons for health disparities in colorectal cancer (CRC) screening, and propose some solutions.


Dr. Lieberman

Issues such as structural racism, socioeconomic status, and lack of health insurance need to be addressed at the societal level. Recent elimination of cost-sharing for colonoscopy after a positive noninvasive screening test, and elimination of cost-sharing for screening exams with polypectomy, reduce financial barriers for those patients who have health care insurance and Medicare.

In addition to the issues raised in this review, other factors could contribute to disparities. CRC screening in rural settings can be challenging because of limited access and transportation issues. In all settings, transportation, time away from work or childcare/adult care responsibilities may be obstacles for individuals with limited resources. Redlining defined where people could live, and reflects structural racism. These housing restrictions may have resulted in environmental exposures (air, water) that could contribute to CRC disparities.

How can practitioners apply this information? Recognition of implicit bias among health care workers is an essential first step toward achieving equity. Providing equitable access to CRC screening works. In a study from Kaiser Permanente (N Engl J Med. 2022;386:796-8), disparities in CRC outcomes between non-Hispanic White versus Black patients were eliminated within 10 years after implementing an annual mailed fecal immunochemical test kit. This is an exciting proof of principle – physicians and health care organizations can reduce health disparities.

David Lieberman, MD, professor of medicine and formerly chief of the division of gastroenterology and hepatology (1997-2021), Oregon Health & Science University, Portland. Dr. Lieberman does not have any relevant disclosures.

PEARLS from the PROS

Incidental hepatic steatosis

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

Nonalcoholic fatty liver disease now dominates the practice of hepatology, and hepatic steatosis may be detected as an incidental finding on imaging despite normal aminotransferase levels. It is important to identify patients at risk of progressive fibrosis.

Calculation of the fibrosis-4 (FIB-4) score (based on age, alanine and aspartate aminotransferase [ALT and AST] levels, and platelet count by the primary care provider, using either an online calculator or the dot phrase ".fib4" in Epic) is a useful first step. If the value is low (with a high negative predictive value for advanced fibrosis), the patient does not need to be referred but can be managed for risk factors for nonalcoholic fatty liver disease. If the value is high, suggesting advanced fibrosis, the patient requires further evaluation. If the value is indeterminate, options for assessing liver stiffness include vibration-controlled transient elastography (with a controlled attenuation parameter to assess the degree of steatosis) and ultrasound elastography.

A low liver stiffness score argues against the need for subspecialty management. An indeterminate score may be followed by magnetic resonance elastography, if available. An alternative to elastography is the enhanced liver fibrosis (ELF) blood test, based on serum levels of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP), and hyaluronic acid.

Published previously in Gastro Hep Advances (doi: 10.1016/j.gastha.2023.03.008).

Dr. Friedman is the Anton R. Fried, MD, chair of the department of medicine at Newton-Wellesley Hospital in Newton, Mass., and assistant chief of medicine at Massachusetts General Hospital, and a professor of medicine at Harvard Medical School and Tufts University, Boston. Dr. Martin is chief of the division of digestive health and liver diseases at the University of Miami, where he is the Mandel Chair of Gastroenterology. The authors disclose no conflicts.


Dr. Friedman


Dr. Martin

Continued from previous page

among Black and Hispanic populations and a lower likelihood of the same populations to receive physician counseling regarding screening.

Barriers to economic stability, including living in impoverished neighborhoods, were also cited as contributors to lower colorectal screening. Patients covered by Medicaid were more than twice as likely as non-Medicaid patients to have suboptimal bowel preparation at screening, the authors noted. Access to transportation remained another frequently observed barrier to completing recommended testing and follow-up.

Mistrust of doctors has been linked to lower screening uptake among Black men. "Longstanding conscious and implicit racism, differences in communication, and socioeconomic context ... engender medical mistrust among racial and ethnic groups," the authors wrote. Reversing it "ultimately requires vast societal change, and we as physicians can facilitate this by encouraging patient-centered discussions that humanize and empower traditionally marginalized populations."

"Longstanding conscious and implicit racism, differences in communication, and socioeconomic context ... engender medical mistrust among racial and ethnic groups," the authors wrote.

Dr. Segura and Dr. Siddique described strategies that have been shown to result in better uptake in specific populations, including removing out-of-pocket costs for screening and follow-up, and designing faith-based or culturally specific outreach delivered through churches and local businesses.

They recommended that researchers change how they study the disparities that bear on colorectal screening and outcomes.

"Collection and use of data on race and ethnicity must be optimized and standardized to ensure that all groups are adequately captured," they wrote. Standardizing self-reporting of race and ethnicity would help address issues of misclassification.

The authors also advised designing studies with longer follow-up, noting that "we must better understand the mechanisms of long-term adherence." Additional research is needed, they said, to evaluate the efficacy of older outreach strategies after societal changes resulting from the COVID-19 pandemic. Efforts to increase the number of Black, Hispanic, Asian, and Alaskan Native/American Indian groups in CRC screening interventions and studies "must be prioritized."

Dr. Segura's and Dr. Siddique's study was funded with grants from the National Institutes of Health. They disclosed no conflicts of interest. ■

Jose Luis Pelaez Inc/Getty Images

Improving patient adherence to IBD treatments begins with these 3 steps

BY WILL PASS
MDedge News

GASTRO HEP ADVANCES

Almost one-third of patients with inflammatory bowel disease (IBD) treated at academic centers with integrated specialty pharmacies may be nonadherent to biologic therapy, resulting in more emergency department visits and hospitalizations, shows a new study published in Gastro Hep Advances (2023 Jan 28. doi: 10.1016/j.gastha.2023.01.016).

Adherence to self-injectable biologic medications is critical, wrote authors who were led by Lauren A. George, MD, of the University of Maryland, Baltimore.

"All healthcare industry stakeholders including healthcare systems, manufacturers, and third-party benefit providers need to understand the importance of improving patient adherence. Decreasing barriers to self-injectable medication acquisition, increasing direct patient interaction with integrated pharmacy teams, and comprehensive patient education are a start to improving patient adherence. In addition, we propose that enhanced care pathways for patients with risk factors for nonadherence would improve adherence and outcomes," they wrote.

The study included 608 patients from 3 clinics who were prescribed self-injectable biologics, including adalimumab, certolizumab, golimumab, and ustekinumab.

Nonadherence became increasingly common in the presence of risk factors such as smoking status, narcotic use, psychiatric history, and prior biologic use. Primary outcomes were medication possession ratio (MPR) and adherence, with nonadherence defined by an MPR lower than 0.86. Secondary outcomes included ED visits and hospitalizations. After a median follow-up period of 903 days, the overall MPR was 0.95, with adherence of 68-70%, which is considered high exceeding previously reported national adherence rates. Patients with all four risk factors had less than 50% adherence. Nonadherence was associated with more ED visits and hospitalizations.

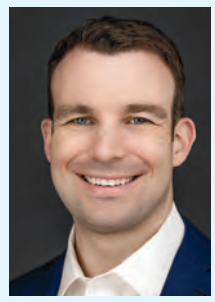
No funding was reported. The investigators disclosed relationships with AbbVie, Janssen, UCB, and others. ■

An important adage in medicine is that medications work only if patients take them. Inflammatory bowel disease is a chronic illness that, if inadequately treated, can lead to emergency department visits, hospitalizations, and surgery.

Injectable biologics are an essential medication to treat inflammatory bowel disease and reduce the side effects that come with corticosteroids.

This study by George et al. showed that patients receiving care at academic medical centers with integrated pharmacies had high adherence to subcutaneous therapies. Unsurprisingly, patients with high adherence had fewer emergency room visits and hospitalizations.

The authors identified risk factors for nonadherence. Among others, opioid use, psychiatric illness, and Medicaid insurance were associated with lower adherence. Identifying patients with these risk factors may allow more intensive outreach to improve adherence. IBD centers with integrated pharmacies, such as those in this study, are likely best equipped to do this. Alternatively, these patients may be best served with infusions that are less frequent than injection and can be regularly scheduled with an appointment.


Dr. Gregory

While this study did not directly compare other practice models, adherence was much higher than in other studies. This suggests the addition of an integrated pharmacy improves adherence and lowers costs. Other factors, such as highly trained IBD gastroenterologists and skilled support staff, may have also helped improve adherence, but in any case the multidisciplinary care, especially integrated pharmacies, should be emulated by other IBD centers.

Martin H. Gregory, MD, MSCI, assistant professor of medicine, Washington University School of Medicine, St. Louis. He disclosed serving on a Bristol Myers Squibb advisory board.

CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

BY JIAYU YAN, MD, WEI CHEN, MD, YAJUN CHEN, MD, PHD

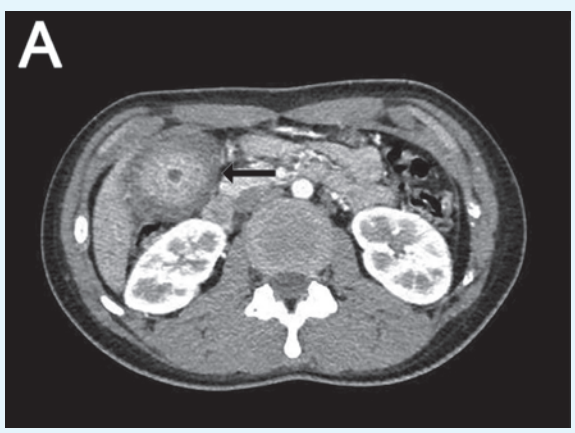
A 15-year-old girl presented with an 18-month history of intermittent right upper quadrant pain that appeared after meals and was relieved after rest. She denied any nausea, vomiting, chills, diarrhea, or constipation. The patient reported no trauma. At admission, physical examination showed tenderness in the right upper abdomen without rebound or guarding. Murphy's sign was also present. The laboratory tests were unremarkable.

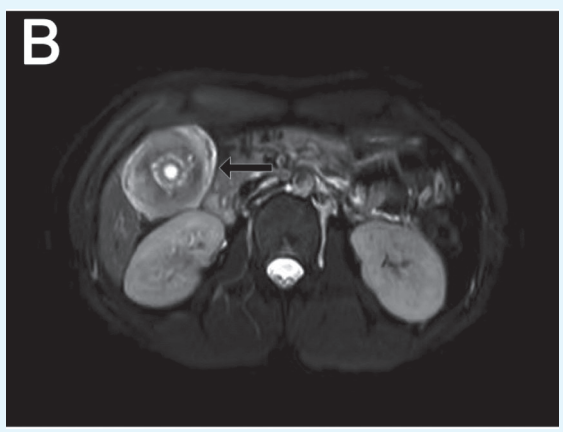
Ultrasound examination indicated gallbladder wall thickening. Furthermore, a contrast-enhanced computed tomographic scan showed marked gallbladder wall thickening with an annular unenhanced proliferative muscularis layer surrounding enhanced proliferative mucosal epithelium (Figure A), and magnetic resonance imaging showed multiple cyst-like spaces in the gallbladder wall (Figures B and C).

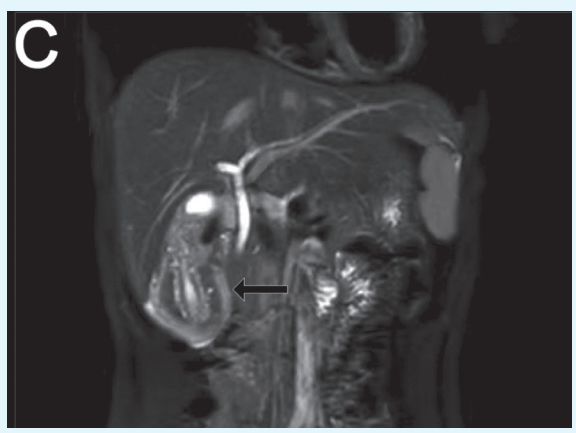
What is the diagnosis, and how should it be managed?

See page 18 for the answer.

Previously published in Gastroenterology (doi: 10.1053/j.gastro.2022.07.013).







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THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

AGA clinical practice update: Best scenarios for endoscopic ultrasound vascular interventions

BY JENNIE SMITH
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Expert treatment centers should consider performing certain endoscopic ultrasound (EUS)-guided vascular interventions with current levels of supporting evidence, according to a practice update from the American Gastroenterological Association.

The AGA Institute's Clinical Practice Update on interventional EUS, published in Clinical Gastroenterology and Hepatology (2023 May 9. doi: 10.1016/j.cgh.2023.03.027), makes the case for broader adoption of two clinically available interventions – EUS-guided coil injection therapy of gastric varices and EUS-guided portosystemic pressure gradient measurement – while listing key research questions that remain to be answered. The update also describes current evidence for several emerging EUS interventions.

The update's authors, led by Marvin Ryou, MD, of Brigham and Women's Hospital, Boston, advised, when available, EUS-guided coil injection therapy of gastric varices over conventional direct endoscopic injection with cyanoacrylate glue, noting that EUS guidance "enhances the precision of injection," expands treatment options to include placement of hemostatic coils, and uses Doppler to provide real-time feedback on hemostasis.


Dr. Ryou

Available evidence suggests that EUS-guided gastric variceal therapy is "safe, with excellent acute hemostasis and low re-bleeding rates, and likely superiority over traditional direct endoscopic glue injection," Dr. Ryou and colleagues wrote in their update. Nonetheless, they cautioned, "the development of a consensus technique would be helpful," better training of technicians is needed, and large, multicenter studies comparing EUS with standard interventional radiology approaches are still needed.

EUS-guided direct measurement of the portosystemic pressure gradient (PPG) may offer improved clinical efficiency over a percutaneous endovascular approach, Dr. Ryou and colleagues determined, notably when there is concern for a pre-sinusoidal cause of portal hypertension. The EUS intervention allows for the "concurrent ability to perform esophagogastroduodenoscopy and EUS as a one-stop shop during which PPG, liver biopsy, and endoscopic features of portal hypertension … can all be evaluated, obtained, and potentially treated during a single procedure."

The authors updated guidance on four emerging interventions for which evidence remains limited: EUS-guided injection therapy of rectal varices, EUS-guided splenic artery embolization, EUS-guided injection therapy in patients with splenic artery pseudoaneurysms, and EUS-guided portal vein sampling. While the last of these interventions appears safe, the authors cautioned, it should be performed only as part of a research protocol.

The authors described an experimental intervention tested in animal models using a EUS-guided intrahepatic portosystemic shunt in which a self-expanding metal stent was deployed via EUS to bridge the hepatic and portal vein and decompress a hypertensive portal system.

The authors cautioned that the guidance was not the product of a formal systematic review, but represented a summary of practical advice gleaned from a literature review to provide practical advice.

The AGA's Clinical Practice Update on interventional EUS makes the case for broader adoption of EUS-guided coil injection therapy of gastric varices and EUS-guided portosystemic pressure gradient measurement.

As a general rule, they said, EUS-guided vascular interventions should be considered when the vascular target occurs in or near the gastrointestinal wall, "which may confer an advantage to an endoscopic rather than percutaneous access," and when the intervention has "a clinical efficacy and safety profile comparable, if not superior, to current alternatives." All the interventions described in the clinical practice update satisfy the first condition, but not the second.

Dr. Ryou and coauthors disclosed consulting fees and research support from device manufacturers. ■

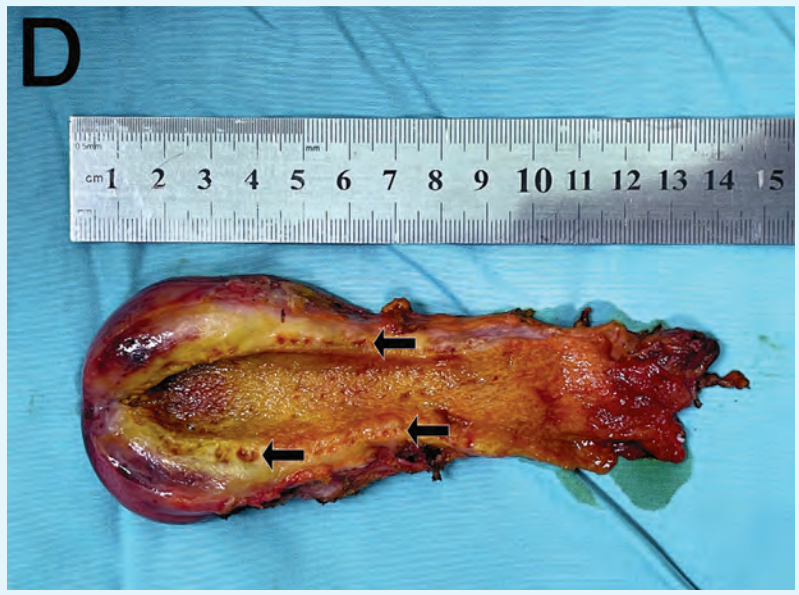
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" from page 16.

Diffuse gallbladder adenomyomatosis

Based on the clinical and imaging findings, a diagnosis of gallbladder adenomyomatosis was made. GA is a benign and usually asymptomatic condition that occurs mainly beyond the age of 50-60 years and is very rare in childhood.[1] Symptomatic gallbladder adenomyomatosis indicates cholecystectomy, considering the presence of inflammation or gallbladder stones.[2] Therefore, a laparoscopic cholecystectomy was performed on our patient. Rokitansky-Aschoff sinuses were seen in the entire thickened gallbladder wall on gross pathologic examination (Figure D). Histopathologic examination confirmed the diagnosis of GA with cholecystitis. The patient was eventually diagnosed with diffuse GA. She was successfully discharged from the hospital 4 days after surgery, and 3 months of follow-up were uneventful.



According to the gross features and areas affected, GA is classified into four types: localized, segmental, annular, and diffuse.[2] To our knowledge, this case presents the most distinguished imaging findings of diffuse GA in the English literature, including the "rosary sign" on contrast-enhanced CT and the "pearl necklace sign" on T2-weighted MRI.[3] Given the problem of difficult visualization of coexisting malignancy, cholecystectomy should be routinely considered for patients with diffuse GA.[2]

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Unveiling the approach to mitigate the impact of NAFLD

BY MAI SEDKI, MD, MPH, AND W. RAY KIM, MD

Nonalcoholic fatty liver disease (NAFLD) has become a rapidly increasing public health burden in the United States and elsewhere. The disease is a manifestation of systemic metabolic abnormalities, including insulin resistance, dyslipidemia, central obesity, and hypertension. In this short review, we summarize data on the burden of NAFLD and its prognostic determinants and review what clinical and public health approaches may be needed to mitigating its impact.

Given the enormous prevalence and increasing public health burden of NAFLD, systematic interventions to mitigate its impact are urgently needed.

Epidemiology of NAFLD

Worldwide, the prevalence of NAFLD is estimated at 6-35%, with biopsy-based studies reporting NASH in 3-5%.[1] U.S. estimates for the prevalence of NAFLD range from 10-46%.[2] In our own analysis of the National Health and Nutrition Examination Survey (NHANES) data, transient elastography-detected steatosis was found in 36%, which projected to a minimum of 73 million American adults.[3]

NAFLD represents a spectrum of disorders ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), the latter leading, in some cases, to progressive hepatic fibrosis and cirrhosis.[4] Out of a large number of subjects with NAFLD, the proportions of NASH patients that develop severe liver problems such as end-stage liver disease (ESLD) or hepatocellular carcinoma (HCC) are progressively smaller. For example, we recently reported that less than 2,000 liver-related deaths are attributable to NAFLD in the U.S. per annum, which corresponds to a crude case fatality rate of < 0.005% per year.[5]

According to the Centers for Disease Control and Prevention, there have been substantial increases in liver-related deaths over the last 2 decades. Mortality from liver disease including hepatobiliary cancers more than doubled from 41,966 deaths (including 15,321 women and 26,645 men) in 2000 to 85,884 deaths (33,000 women and 52,884 men) in 2020. The proportion of deaths specifically attributed to NAFLD among liver-related deaths was miniscule in 2000, accounting for 1.1% in women and 0.7% in men. By 2020, the proportions increased several folds in both sexes (7.4% in women and 2.7% in men).[6] Moreover, it is likely that a substantial portion of deaths from chronic liver disease from unknown causes ("cryptogenic") are likely end-stage NAFLD, making these figures underestimates of the true impact of NAFLD in the U.S.

From a comparative epidemiologic perspective, there are significant racial and ethnic and socioeconomic disparities in NAFLD prevalence, wherein Hispanic persons and individuals experiencing food insecurity – independent of poverty status, education level, race, and ethnicity – are disproportionately more affected by NAFLD.[7,8] Furthermore, these disparities persist when examining long-term complications of NAFLD, such as developing HCC.

Prognosis in NAFLD: NASH versus fibrosis

Given the enormous prevalence and increasing public health burden of NAFLD, systematic interventions to mitigate its impact are urgently needed. Clearly, patients who already have developed advanced liver disease need to be directed to specialty care so the disease progression may be halted and complications of ESLD may be prevented or managed. On the other hand, in order to mitigate the future impact of ESLD, prompt identification of at-risk patients and proactive interventions to improve liver health are needed.

In the assessment of disease progression, prior data have shown that the presence of NASH and increasing stages of liver fibrosis are important predictors of disease progression. Fibrosis is a component of NASH, while NASH is thought to be a prerequisite for fibrosis. In a prospective, multicenter follow-up study of NAFLD evaluated by liver biopsies (n = 1,773), over a median follow-up of 4 years, 37 (2%) developed hepatic decompensation, while 47 (3%) died from any cause, which included ESLD (n = 12), cardiovascular complications (n = 4), and malignancies (n = 12), including HCC (n = 9).[9] It is not entirely surprising that advanced fibrosis and cirrhosis was highly associated with the development of hepatic decompensation. In their multivariable analysis, patients with F3-4 had a 13.8-fold (95% confidence interval [CI]: 4.6, 41.0) increase in the hazard of reaching a MELD score of 15 compared to those with F0-2. In addition, all-cause mortality was 17.2-fold (95% CI: 5.2, 56.6) higher with F3-4 compared to F0-2.

These data have been borne out by a larger body of literature on the topic. In a recent meta-analysis assessing the relation between liver fibrosis and future mortality, which included 17,301 subjects with NAFLD, patients with at least stage 2 fibrosis experience a significantly increased risk of liver-related and overall mortality, a trend that accelerates at higher fibrosis stages.[10] These point to liver fibrosis as the singular determinant of long-term prognosis, in comparison, for example, with the diagnosis of NASH. Hagström et al. conducted a retrospective cohort study of patients with biopsy-proven NAFLD in Sweden. When fibrosis stage and histological diagnosis of NASH were considered together, NASH did not have an impact on overall mortality (hazard ratio [HR] = 0.83, P = .29) or liver morbidity (HR = 0.62, P = .25).[11]

On an individual level, factors that affect fibrosis progression are not as well studied. It is commonly believed that demographic factors (e.g., age, sex, and race), genetic polymorphisms (e.g., PNPLA3,

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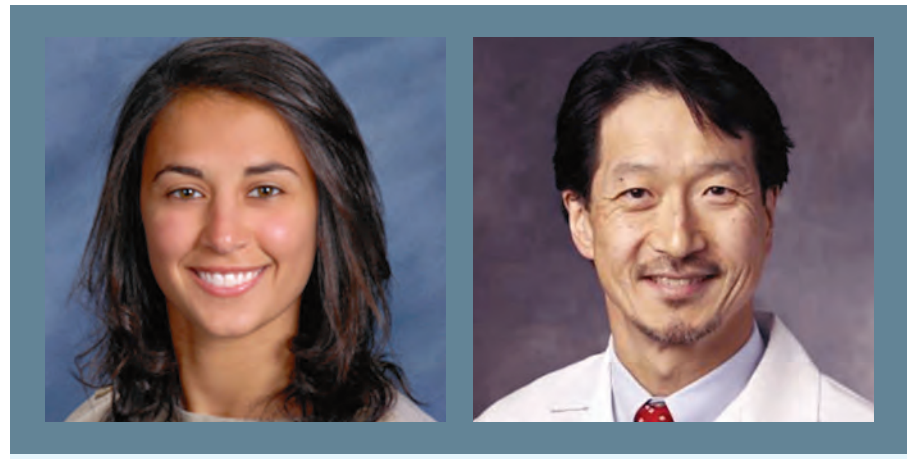

Mai Sedki, MD, MPH, is a doctoral candidate at the University of California, San Francisco. **W. Ray Kim, MD,** is professor of medicine (gastroenterology and hepatology) at Stanford University in California.

The health care burden of non-alcoholic fatty liver disease (NAFLD) in the United States is increasing. Recognition and care of NAFLD may initially start with primary care physicians and general gastroenterologists. In this issue of In Focus, Drs. Mai Sedki and W. Ray Kim from Stanford University review the initial determination of non-alcoholic steatohepatitis (NASH) and fibrosis, methods of assessing fibrosis for risk stratification, and risks of hepatocellular carcinoma among this patient population.

Judy A. Trieu, MD, MPH
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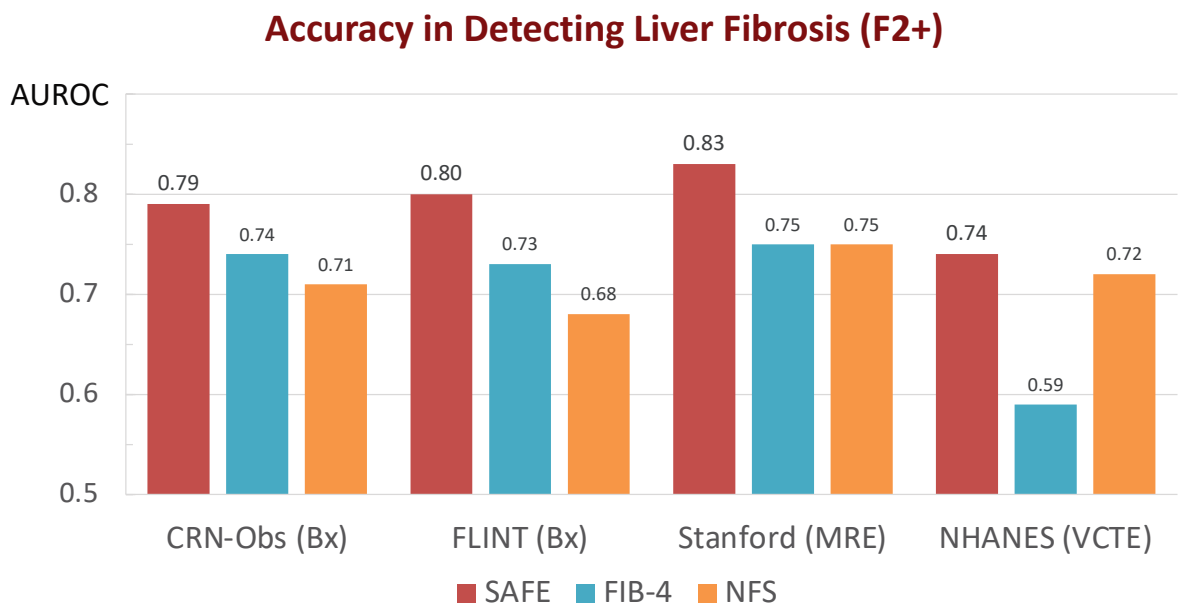
Figure 1. Comparison of 3 blood test-based fibrosis markers (Fib-4,NFS, and SAFE scores) in the detection of fibrosis stage 2 or higer.



CRN: Clinical Research Network; FLINT: Farnesoid X nuclear receptor ligand obeticholic acid for noncirrhotic NASH; SAFE: Steatosis-associated fibrosis estimator; FIB-4: Fibrosis index-based on 4 factors; NFS: Non-alcoholic fatty liver disease fibrosis score; Bx: biopsy; MRE: Magnetic resonance elastography; VCTE: Vibration-controlled transient elastography

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TM6SF2), clinical comorbidities (e.g., obesity, DM, and sleep apnea), and environmental factors (e.g., smoking) may accelerate fibrosis and disease outcomes, although prospective data are sparse to estimate the extent these individual variables affect progression.[12] Recent guidelines remain silent about whether and how these data may be incorporated in screening for NAFLD in the population.

Assessment of liver fibrosis

The traditional means to detect liver fibrosis is liver histology, which also assesses steatosis, individual components of NASH and, often importantly, other concomitant liver pathology. In reality, however, liver biopsies have several limitations including the risk of complications, patient discomfort, economic costs, and sampling variability. Increasingly, "noninvasive" methods have been used to estimate liver fibrosis in patients with NAFLD. Liver elastography estimates the physical stiffness of the organ, which may be measured by MRI or ultrasound. Among ultrasound-based technologies, vibration-controlled transient elastography (VCTE) is more widely accepted and affordable although it may not be as accurate as MR elastography.[13]

In general, these elastographic tests are not readily accessible to most physicians outside hepatology specialty practices. Instead, blood test-based markers have been developed and widely recommended as the initial modality to assess liver fibrosis. Figure 1 represents a partial list of blood test-based markers. Traditionally, FIB-4 and NFS have been considered the most widely recommended by society guidelines. The AGA Pathway for evaluation of patients with NAFLD recommends first to apply the FIB-4 score and, in patients considered to be at intermediate risk of fibrosis for advanced fibrosis (stage 3 or 4, FIB-4 = 1.3-2.67), to assess liver stiffness by VCTE.[14]

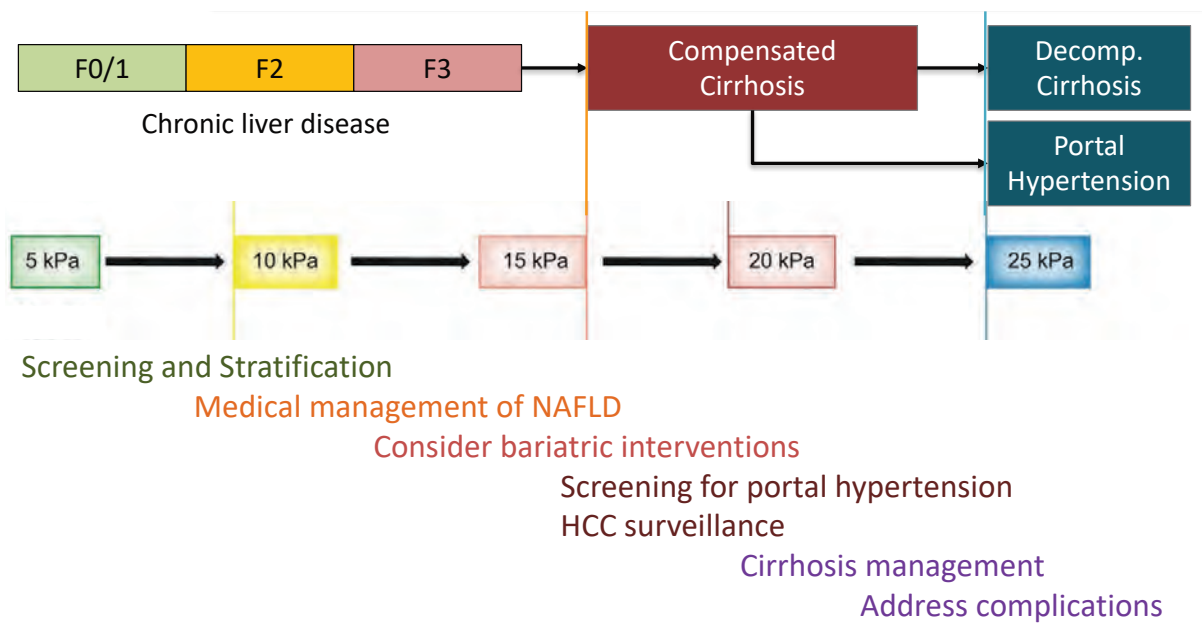
More recently, the accumulating natural history data have highlighted the inflection in the risk of future outcomes coinciding with F2 and therapeutic trials that target patients with "at risk NASH," thus more attention has been paid to the identification of patients with stage 2 (or higher). The steatosis-associated fibrosis estimator (SAFE) was developed for this specific purpose (http://medcalculators.stanford.edu/safe). The score has been validated in multiple data sets, in all of which SAFE outperformed FIB-4 and NFS (Figure 1). When the score was applied to assess overall survival in participants of the NHANES, patients with NAFLD deemed to be high risk (SAFE > 100) had significantly lower survival (37% Kaplan-Meier survival at 20 years), compared to those with intermediate (SAFE 0-100, 61% survival) and low (SAFE < 0, 86% survival). In comparison, the 20-year survival of subjects without NAFLD survival was 79%.[15]

Regardless of the modality for initial stratification, it is widely accepted that mechanical elastography constitutes the next step in prognosticating the patient. In the AGA Pathway, liver stiffness of < 8 kPa is considered low risk, which corresponds in most analysis with lack of stage 2 fibrosis, whereas stiffness of > 12 kPa may be indicative of stage 3 or 4. These recommendations are consistent with those from the latest Baveno Consensus Conference ("Baveno 7"). Figure 2 expands on the so-called "rule of 5" from the consensus document and correlates liver stiffness (by VCTE) with progression of liver fibrosis as well as clinical presentation. For example, liver stiffness < 15 kPa is associated with a low risk of clinically significant portal hypertension (CSPH). Similarly, in patients with a normal platelet count (>150,000/mm^3) and liver stiffness < 20 kPa, the probability of gastroesophageal varices is sufficiently low that a screening endoscopy may be avoided. On the other hand, liver stiffness > 25 kPa is associated with increasing risk of decompensated cirrhosis and portal hypertension.[16]

Partnership between primary care and specialists

The insights expressed in Figure 2 can be utilized to guide management decisions. In patients without evidence of liver fibrosis, emphasis may primarily be on screening, stratification, and management of metabolic syndrome. For patients with evidence of incipient liver fibrosis, medical management of NAFLD needs to be implemented including lifestyle changes and pharmacological interventions as appropriate. For patients unresponsive to medical therapy, an endoscopic or surgical bariatric procedure should be considered. Management of patients with evidence of cirrhosis includes screening for portal hypertension, surveillance for HCC, medical management of cirrhosis, and finally, in suitable cases, referral for liver transplant evaluation. The reader is referred to the latest treatment guidelines for detailed discussion of these individual management modalities [ref, AGA and AASLD guidelines].[14,17]

Figure 2. NAFLD management cascade. Liver stiffness measurement with transient elastography helps assess fibrosis stage, anticipate clinical presentations and guide management.



Graphics courtesy Mai Sedki, MD, MPH, and W. Ray Kim, MD

Given the spectrum of management modalities needed to successfully manage patients with NAFLD, it is unrealistic to expect that hepatologists and gastroenterologists are able to manage the large number of patients with NAFLD. In general, clinical activities on the left side of Fgure 2 are in the domain of primary care providers, whereas management of patients with progressive liver fibrosis is conducted by the specialist. An important aspect of the overall management of these patients is risk management in terms of the metabolic syndrome, including cardiovascular risk reduction and diabetes management, as appropriate. Many patients with NAFLD are burdened with several comorbidities and likely to benefit from a multidisciplinary team consisting of primary care, endocrinology, preventive cardiology, pharmacy, nutrition/dietetics, social services, and addiction specialists, as well as hepatology and gastroenterology. Prospective, high-quality data to define these teams and their function are yet to be generated.

Conclusion

NAFLD is an important and increasing public health concern in the U.S. Once diagnosed, assessing liver fibrosis and evaluating the presence of the components of metabolic syndrome in these patients constitute the key components in the care in terms of risk stratification, medical management, and referral decisions. Noninvasive tests have been increasingly utilized including liver stiffness measurements and various blood test-based indicators. For patients in specialty GI/hepatology care, transient elastography is a widely accepted tool, with which standardized recommendations may be made for screening, stratification, and medical and surgical interventions in patients with NAFLD. ■

Address correspondence to wrkim@stanford.edu. The authors disclosed no conflicts of interest. Twitter: @SedkiMD and @WRayKimMD.

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AGA Postgraduate Course

Advances in pancreaticobiliary disease interventions: More options and better outcomes

BY ALLISON R. SCHULMAN, MD, MPH

Advances in pancreaticobiliary disease interventions were reviewed at Digestive Disease Week in May as part of the American Gastroenterological Association postgraduate course.

The endoscopic treatment of pancreaticobiliary disease has advanced exponentially. Endoscopic interventions have markedly decreased the need for percutaneous and surgical procedures. Evidence-based advances are changing the landscape of pancreaticobiliary disease management.

Dr. Schulman

While endoscopic retrograde cholangiopancreatography (ERCP) with transpapillary stent placement is first-line for the treatment of biliary obstruction, endoscopic ultrasound (EUS)-guided biliary drainage has emerged as an effective alternative in cases of failed ERCP. These procedures can be performed via a transhepatic approach (hepaticogastrostomy) from the proximal stomach, an extrahepatic approach (choledochoduodenostomy) from the duodenum, or via the gallbladder. Numerous studies have proved the safety and efficacy of these interventions in malignant biliary obstruction. A recent systematic meta-analysis pooled all of these approaches and concluded that EUS-guided biliary drainage is also reasonable to offer in benign disease when ERCP has failed or is not technically possible.

EUS-guided gallbladder drainage is similarly emerging as an alternative approach for management of acute cholecystitis. This is a reasonable option in patients with acute cholecystitis who are poor surgical candidates, have no evidence of gallbladder perforation, and will tolerate sedation. This approach may be preferred over ERCP with cystic duct stent placement in the setting of a large stone burden, gastric outlet obstruction, or when an indwelling metal biliary stent occludes the cystic duct. Multidisciplinary discussion with surgical and interventional radiology services is essential, especially given this technique may preclude future cholecystectomy.

Indeterminate biliary strictures historically pose a major diagnostic challenge, and current approaches in the evaluation of such strictures lack diagnostic sensitivity. ERCP with concurrent brushing of the bile duct for cytology remains the most commonly used method of acquiring tissue. However, the sensitivity of diagnosis on brush cytology remains frustratingly low. Recent compelling evidence for increasing the number of brush passes to 30 in an indeterminate stricture improves diagnostic sensitivity and is a simple, safe, and low-cost intervention. This approach may ultimately decrease the number of patients requiring surgical intervention, which is particularly important when up to one-fifth of suspected biliary malignancies are found to be benign after surgical resection.

The treatment of biliary strictures has also evolved. Various stents are available, and different practice patterns have emerged for management of this entity. In an updated meta-analysis of randomized controlled trials evaluating multiple plastic stents versus a single covered metal stent for benign biliary strictures, no difference was found in stricture resolution, stricture recurrence, stent migration, or adverse events. However, those patients treated with covered metal stents required fewer sessions of ERCP for stricture resolution. Moreover, no difference in stricture resolution was seen in subgroup analysis between anastomotic strictures, chronic pancreatitis, or bile duct injury. Despite higher cost of the stent itself, covered metal stents may ultimately lead to an overall decrease in health care expenditure. The above examples are only a small subset of the progress that has been made in endoscopic management of pancreaticobiliary disease. The armamentarium of tools and techniques will continue to evolve to help us provide better minimally invasive care for our patients. ■

Dr. Schulman is the incoming chief of endoscopy and director of bariatric endoscopy at Michigan Medicine. She disclosed consultancy work with Apollo Endosurgery, Boston Scientific, Olympus, and MicroTech, and research support from GI Dynamics and Fractyl.

AGA Postgraduate Course

Eosinophilic esophagitis: A year in review

BY JOAN W. CHEN, MD, MS

It has been a prolific year in eosinophilic esophagitis (EoE) research, particularly of high-impact clinical trials that will alter the current management paradigm. At the AGA Postgraduate Course in May, we highlighted recent noteworthy randomized controlled trials (RCT) using eosinophil-targeting biologic therapy, esophageal-optimized corticosteroid preparations, and dietary elimination in EoE.

Dr. Chen

Dupilumab, a monoclonal antibody that blocks interleukin-4 and IL-13 signaling, was tested in a phase 3 trial for adults and adolescents with EoE.[1] In this double-blind, randomized, placebo-controlled trial, the efficacy of subcutaneous dupilumab 300 mg weekly or every other week was compared against placebo. Stringent histologic remission (≤ 6 eosinophils/high power field) occurred in approximately 60% who received dupilumab (either dose) versus 5% in placebo. However, significant symptom improvement was seen only with 300 g weekly dupilumab.

On the topical corticosteroid front, the results of two RCTs using fluticasone orally disintegrating tablet (APT-1011) and budesonide oral suspension (BOS) were published. In the APT-1011 phase 2b trial, patients were randomized to receive 1.5 mg or 3 mg daily or b.i.d. versus placebo for 12 weeks.[2] High histologic response rates and improvement in dysphagia frequency were seen with all ≥ 3-mg daily-dose APT-1011, compared with placebo. However, adverse events (i.e. candidiasis) were highest among those on 3 mg b.i.d. Thus, 3mg daily APT-1011 was thought to offer the most favorable risk-benefit profile. In the BOS phase 3 trial, patients were randomized 2:1 to received BOS 2 mg b.i.d. or placebo for 12 weeks.[3] BOS was superior to placebo in histologic, symptomatic, and endoscopic outcomes. Diet remains the only therapy targeting the cause of EoE and offers a potential drug-free remission. In the randomized, open label trial of 1- versus 6-food elimination diet, adult patients were allocated 1:1 to 1FED (animal milk) or 6FED (animal milk, wheat, egg, soy, fish/shellfish, and peanuts/tree nuts) for 6 weeks.[4] No significant difference in partial or stringent remission was found between the two groups. Step-up therapy resulted in an additional 43% histologic response in those who underwent 6FED after failing 1FED, and 82% histologic response in those who received swallowed fluticasone 880 mcg b.i.d after failing 6FED. Hence, eliminating animal milk alone in a step-up treatment approach is reasonable.

We have witnessed major progress to expand EoE treatment options in the last year. Long-term efficacy and side-effect data, and studies comparing between therapies are needed to improve shared decision-making and strategies to implement tailored care in EoE. ■

Dr. Chen is a clinical assistant professor in gastroenterology with the University of Michigan. She disclosed consultancy work with Phathom Pharmaceuticals. For references, see https://shorturl.at/epK48.

AGA Postgraduate Course

Celiac disease: Update on diagnosis and monitoring

BY CAROL SEMRAD, MD

Celiac disease clinical practice and guideline updates were featured in the Stomach & Small Bowel Post Graduate Course at DDW 2023. Celiac disease is a small bowel disorder. Specific antibodies along with a duodenal biopsy allow a secure diagnosis of celiac disease. Case detection rates have improved but many patients remain undiagnosed. The only treatment available at present is a gluten-free diet (GFD). Most patients respond clinically to a GFD but histologic recovery is not always complete and may result in clinical consequences.


Dr. Semrad

The anti-tissue transglutaminase IgA test (tTg-IgA) is the best initial serology test. A total IgA level appropriate for age is required to interpret a negative result. In patients with IgA deficiency, the deamidated gliadin peptide (DGP) and/or tTg-IgA antibodies, may be helpful for diagnosis along with a duodenal biopsy. First-degree female relatives with homozygous DQ2 positivity are at highest risk.

Both serology and duodenal biopsy have pitfalls in the diagnosis of celiac disease. In European studies of children, the diagnosis is secure with a tTg-IgA antibody of at least 10 times the upper limit of normal (≥10×ULN) and positive endomysial antibody (EMA) on a separate day. There are fewer data on the correlation of tTg-IgA ≥10×ULN positive with villous atrophy in adults. Most require biopsy for diagnosis.

Considerations to forgo biopsy in adults include: tTg-IgA of ≥10×ULN positive in patients following a GFD, or otherwise unable to undergo endoscopy with duodenal biopsy, or shared decision-making. Celiac disease recovery is assessed by clinical response to a GFD and antibody conversion to negative, which does not always correlate with histology. Clinical consequences of persistent villous atrophy include increased risks for lymphoproliferative malignancy, hip fracture, and refractory celiac disease. ■

Dr. Semrad is director of the small bowel disease and nutrition program at the University of Chicago Medicine. She disclosed no conflicts of interest. References: shorturl.at/sKL13

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