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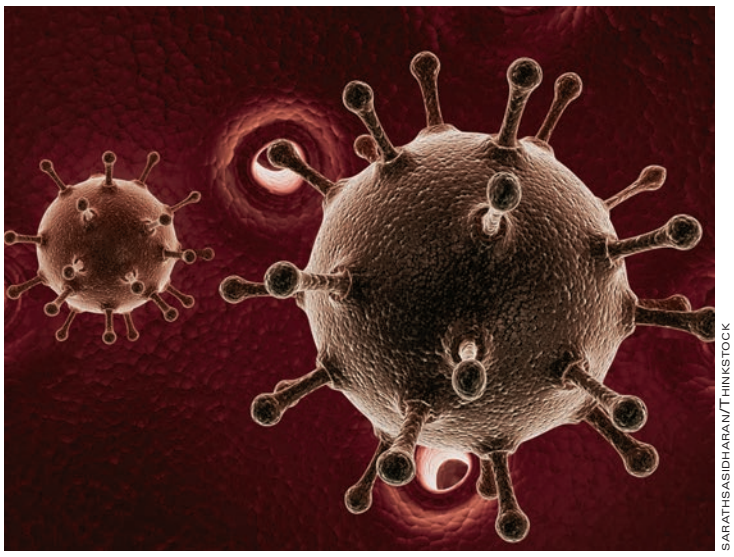

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In its first HBV screening guidelines update since 2008, the CDC now says risk-based testing alone is not enough.

CDC recommends screening all adults for hepatitis B

BY LUCY HICKS

All adults should be tested for hepatitis B virus (HBV) at least once in their lifetime, according to updated guidelines from the Centers for Disease Control and Prevention.

This is the first update to HBV screening guidelines since 2008, the agency said.

"Risk-based testing alone has not identified most persons living with chronic HBV infection and is considered inefficient for providers to implement," the authors wrote in the new guidance, published in the CDC's Morbidity and Mortality Weekly Report. "Universal screening of adults for HBV infection is cost-effective, compared with risk-based screening and averts liver disease and death. Although a curative treatment is not yet available, early diagnosis and treatment of chronic HBV infections reduces the risk for cirrhosis, liver cancer, and death."

Howard Lee, MD, an assistant professor in the section of gastroenterology

See **Hepatitis B** · *page 5*

Vedolizumab found effective for chronic pouchitis

The drug may fill 'large unmet need'

BY CAROLYN CRIST

Vedolizumab appears to be effective at reducing intestinal inflammation and inducing remission in patients who developed chronic pouchitis after undergoing ileal pouch–anal anastomosis (IPAA) for ulcerative colitis, according to a phase 4 trial.

The incidence of modified Pouchitis Disease Activity Index (mPDAI)–defined remission after 14 weeks was 31% for vedolizumab, compared with 10% for placebo.

"Vedolizumab works in both ulcerative colitis and Crohn's disease, so it appeared rational to test its efficacy in chronic, antibiotic-resistant pouchitis," lead author Simon Travis, DPhil, professor of clinical gastroenterology at the University of Oxford's Kennedy Institute of Rheumatology and Translational Gastroenterology Unit in the United Kingdom, said in an interview.

"Vedolizumab works for antibiotic-resistant pouchitis," he said. "It is the first advanced therapy licensed for chronic pouchitis in Europe and can be a game changer for patients who develop pouchitis after experiencing ulcerative colitis severe enough to need colectomy who might

See **Vedolizumab** · *page 6*

Pillbot wins AGA Shark Tank contest

BY LAIRD HARRISON

MDedge News

SAN FRANCISCO – No one yet has figured out how to shrink doctors so they can make house calls inside the human blood stream as they did in the science fiction movie "Fantastic Voyage." But the founders of a gastroenterology start-up think they have the next best thing – a remote-controlled robot so small it can be swallowed like a pill.

The concept captured the imagination of a panel of judges earlier this month at the 2023 American Gastroenterological Association Tech Summit where it was named the winner of the annual Shark Tank innovation competition. The AGA Tech Summit and Shark Tank are the flagship events of the AGA Center

See **Robot pill** · *page 7*

INSIDE

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LETTER FROM THE EDITOR

Chronicling gastroenterology's history

Each May, the gastroenterology community gathers for Digestive Disease Week® to be inspired, meet up with friends and colleagues from across the globe, and learn the latest in scientific advances to inform how we care for our patients in the clinic, on inpatient wards, and in our endoscopy suites. DDW® 2023, held in the Windy City of Chicago, does not disappoint. This year's conference features an array of offerings, including 3,500 poster and ePoster presentations and 1,300 abstract lectures, as well as the perennially well-attended AGA Post-Graduate Course.


Dr. Adams

This year's AGA Presidential Plenary, hosted on May 8 by outgoing AGA President Dr. John M. Carethers, is not to be missed. The session will honor the 125-year history of the AGA and recognizes the barriers overcome in diversifying the practice of gastroenterology. You will learn about individuals such as Alexis St. Martin, MD; Basil Hirschowitz, MD, AGAF; Leonidas Berry, MD; Sadye Curry, MD; and, other barrier-breakers in GI who have been instrumental in shaping the modern practice of gastroenterology. I hope you will join me in attending.

In this month's issue of GIHN, we introduce the winner of the 2023 AGA Shark Tank innovation competition, which was held during the 2023 AGA Tech Summit. We also report on a landmark phase 4, double-blind randomized trial published in the New England Journal of Medicine demonstrating the effectiveness of vedolizumab in inducing remission in chronic pouchitis, and a new AGA clinical practice update on the role of EUS-guided gallbladder drainage in acute cholecystitis.

The AGA Presidential Plenary will honor the 125-year history of the AGA and recognize barriers overcome in diversifying GI practice.

The AGA Government Affairs Committee also updates us on their advocacy to reform prior authorization policies affecting GI practice, and explains how you can assist in these efforts. In our Member Spotlight, we introduce you to gastroenterologist Sharmila Anandasabapathy, MD, who shares her passion for global health and the one piece of career advice she's glad she ignored.

Finally, GIHN Associate Editor Dr. Avi Ketwaroo presents our quarterly Perspectives column highlighting differing approaches to clinical management of pancreatic cystic lesions. We hope you enjoy the exciting content featured in this issue and look forward to seeing you in Chicago (or, virtually) for DDW. ■

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

Universal screening

Hepatitis B *from page 1*

and hepatology at Baylor College of Medicine in Houston, agreed that risk-based screening has not been effective. A universal screening approach "is the way to go," he said. With this new screening approach, patients can get tested without having to admit that they may be at risk for a chronic disease like HIV and HBV, which can be stigmatizing, said Dr. Lee, who was not involved with making these recommendations.

An estimated 580,000 to 2.4 million individuals are living with HBV infection in the United States, and two-thirds may be unaware they are infected, according to the CDC. The virus spreads through contact with blood, semen, and other body fluids of an infected person.

The guidance now recommends using the triple panel (HBsAg, anti-HBs, total anti-HBc) for initial screening.

"It can help identify persons who have an active HBV infection and could be linked to care; have resolved infection and might be susceptible to reactivation (for example, immunosuppressed persons); are susceptible and need vaccination; or are vaccinated," the authors wrote.

Patients with previous HBV infection can have the infection reactivated with immunosuppressive treatments, Dr. Lee said, which is why detecting prior infection via the triple panel screening is important.

Women who are pregnant should be screened, ideally, in the first trimester of each pregnancy, regardless of vaccination status or testing history. If they have already received timely triple

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978-356-0032 cwall@mdedge.com

Editorial Offices 2275 Research Blvd, Suite 400, Rockville, MD 20850, 973-206-3434
E-mail ginews@gastro.org

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Chronic pouchitis

Vedolizumab *from page 1*

have thought that surgery would be the ultimate solution."

The study was published online (2023 Mar 30. doi: 10.1056/NEJMoa2208450) in The New England Journal of Medicine.

Treating chronic pouchitis

About half of patients with ulcerative colitis who undergo restorative proctocolectomy with IPAA will develop pouchitis within 5 years, the authors write. Among those, about one-fifth will have chronic pouchitis, with symptoms that last longer than 4 weeks. Symptoms include increased stool frequency, abdominal pain, fecal urgency, and impaired quality of life.

Typically, antibiotics are recommended as first-line treatment for acute pouchitis, but antibiotic resistance is common. Previous studies have suggested that tumor necrosis factor antagonists and the monoclonal antibodies vedolizumab and ustekinumab may be effective in pouchitis that is refractory to antibiotics.

The U.S. Food and Drug Administration has approved vedolizumab as a treatment for moderate to severe ulcerative colitis and Crohn's disease. In early 2022, the European Commission approved vedolizumab for adult patients with moderate to severe active chronic pouchitis who had undergone proctocolectomy with IPAA and had an inadequate response to antibiotic therapy. The approval was based on results from the EARNEST trial.

As part of the EARNEST trial, Dr. Travis and colleagues at 31 sites in North America and Europe conducted a phase 4, double-blind, randomized trial to evaluate vedolizumab for chronic pouchitis after IPAA for ulcerative colitis.

Between October 2016 and March 2020, researchers identified 102 adult patients who met the study criteria. They were eligible if they had undergone proctocolectomy at least 1 year before screening and had active chronic pouchitis, which was defined by an mPDAI score of 5 or more and a minimum subscore of 2 on the endoscopic domain.

After a 28-day screening period, patients were randomly assigned in a 1:1 ratio to receive 300 mg of intravenous vedolizumab or placebo on day 1 and at weeks 2, 6, 14, 22, and 30. All patients also received 500 mg of oral ciprofloxacin twice daily from weeks 1 to 4. Additional courses of antibiotics were allowed, as needed, for pouchitis flares that occurred after week 14.

The primary endpoint was mPDAI-defined remission, or an mPDAI score of 4 or less and a reduction of 2 or more points on the 12-point scale at week 14.

Antibiotics are typically recommended as first-line treatment for acute pouchitis, but antibiotic resistance is common.

Other endpoints included mPDAI-defined remission at week 34, mPDAI-defined response (a reduction of 2 or more points) at weeks 14 and 34, and PDAI-defined remission (a PDAI score of 6 or less and a reduction of 3 or more points on the 18-point scale) at weeks 14 and 34. The mPDAI is based on clinical symptoms and endoscopic findings, whereas the PDAI is based on clinical symptoms, endoscopic findings, and histologic findings.

Overall, 36 patients (71%) in the vedolizumab group and 32 patients (63%) in the placebo group completed treatment and received all infusions through week 30. Eight patients in each group discontinued vedolizumab or placebo owing to a lack of efficacy. Demographic and clinical characteristics were similar in the two groups – about 84% of the patients were White, and the majority were men.

At the 14-week mark, 16 of 51 patients (31%) in the vedolizumab group and 5 of 51 patients (10%) in the placebo group achieved mPDAI-defined remission (a 21–percentage point difference; 95% confidence interval, 5-38; $P = .01$). At week 34, 35% of the vedolizumab group and 18% of the placebo group reached remission. A post hoc analysis found that a high percentage of patients in the vedolizumab group reached remission regardless of whether concomitant antibiotics were used before week 14 or 34.

"Concomitant antibiotic use after week 4 was reported in a higher percentage of patients in the vedolizumab group than in the placebo group, a finding that was unexpected," the authors write. "However, the use of additional antibiotics was not considered to be a treatment failure because antibiotics are the current standard of care for chronic pouchitis."

Additional findings

Vedolizumab showed major differences in the other endpoints as well. The percentage of patients with PDAI-defined remission was 35% in the vedolizumab group versus 10% in the placebo group at week 14, and 37% versus 18% at week 34.

The percentage of patients with mPDAI-defined response at week 14 was 63% among the vedolizumab group and 33% among the placebo group. By week 34, the between-group difference was 51% versus 29%.

Vedolizumab also showed greater changes in total PDAI scores, including endoscopic and histologic subscores, as well as remission and response defined by the Inflammatory Bowel Disease Questionnaire (IBDQ). However, there were no significant differences in changes from baseline for the IBDQ or the Cleveland Global Quality of Life (CGQL) score.

The vedolizumab group had a higher percentage of patients with sustained mPDAI-defined remission (difference, 22 percentage points; 95% CI, 6-37) and sustained PDAI-defined remission (difference, 23 percentage points; 95% CI, 8-39).

Adverse events were reported in 47 patients (92%) in the vedolizumab group and 44 patients (86%) in the placebo group. Pouchitis was reported as an adverse event in 24 patients (47%) in the vedolizumab group and 20 patients (39%) in the placebo group. More patients in the vedolizumab group also reported upper respiratory tract infections and headaches.

Serious adverse events occurred in three

Continued on following page

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panel screening for hepatitis B and have no new HBV exposures, pregnant women need only HBsAg screening, the guidelines state.

The guidelines highlight higher risk groups, specifically those who are incarcerated or formerly incarcerated; adults with current or past hepatitis C virus infection; those with current or past sexually transmitted infections; and, those with multiple sex partners.

People who are susceptible for infection, refuse vaccination, and are at higher risk for HBV should be screened periodically, but how often they should be screened should be based on shared decision-making between the provider and patient as well as individual risk and immune status.

Additional research into the optimal frequency of periodic testing is necessary, the authors say.

"Along with vaccination strategies, universal screening of adults and appropriate testing of persons at increased risk for HBV infection will improve health outcomes, reduce the prevalence of HBV infection in the United States, and advance viral hepatitis elimination goals," the authors wrote.

The new recommendations now contrast with the 2020 screening guidelines issued by the U.S. Preventive Services Task Force (USPSTF) that recommend risk-based screening for hepatitis B.

"When that recommendation was published, the Task Force was aligned with several other organizations, including the CDC, in supporting screening for hepatitis B in high-risk populations — and importantly, we're all still aligned in making sure that people get the care that they need," said Michael Barry, MD, chair of the USPSTF, in an emailed statement. "The evidence on clinical preventive services is always changing, and the Task Force aims to keep all recommendations current, updating each recommendation approximately every 5 years."

"In the meantime, we always encourage clinicians to use their judgment as they provide care for their patients — including those who may benefit from screening for hepatitis B — and to decide together with each patient which preventive services can best help them live a long and healthy life," Dr. Barry said.

The American Association for the Study of Liver Diseases is currently updating HBV screening recommendations, said Dr. Lee who expects other professional societies to follow the CDC recommendations.

"It's not uncommon that we see the CDC or societies making recommendations and the USPSTF following along, so hopefully that's the case for hepatitis B as well," he said.

The authors reported no potential conflicts of interest. ■

Motorized pill

Robot pill *from page 1*

for GI Innovation and Technology.

"This could be a game-changing investment down the line," one of the judges, Amrita Sethi, MD, MSc, AGAF, from Columbia University Medical Center in New York, said in an interview.

Hawyard, Calif.–based Endiatx is early in its voyage. The disposable motorized pill, called PillBot, swims through the stomach beaming video back to its operators, but CEO Torrey Smith, an aerospace engineer, sees future generations of the device operating on any diseased tissues that can be treated with surgery. "We believe teeny robots can go anywhere in the body," he said.

The company executives envision that one day, robots small enough to enter the human brain will be able to eat away at tumors. "Imagine having your brain surgery while you're on a ride at Disneyland," said Endiatx cofounder and chair Alex Luebke. If that sounds fanciful, Mr. Smith cites a case report of a botfly larva that wormed its way into a human skull and ate a golf ball–sized chunk of brain.

Endiatx has raised $3 million and sent 24 of its robots swimming into the stomachs of its founding team. Mr. Smith himself has swallowed 15. Operators can use an external device with a joystick. Engineers have experimented with an Xbox video game controller to navigate around the stomach. The procedure requires no anesthesia.

The company expects to apply for Food and Drug Administration approval in 2025 or 2026. Mr. Smith is hoping the agency will approve it quickly because the robot pills are similar enough to passive camera pills that have been on the market for years.

But he also sees it as a crucial step forward because controlling the robot with three electric motors squirting water in six directions will allow physicians to point it at what they really need to see, not just hope to get a lucky shot of a problem area as the device floats by.

COURTESY AGA

Endiatx won the top spot in the Shark Tank contest at the 2023 AGA Tech Summit back in March. Pictured are: Sri Komanduri, MD, AGAF, chair, AGA Center for GI Innovation and Technology; Torrey Smith, Endiatx co-founder and CEO; Amrita Sethi, MD, MSc, AGAF, chair-elect, AGA Center for GI Innovation and Technology.

The most immediate technical challenge is improving the quality of the pill's video. "We're evaluating different cameras but we know we can't be inferior on the imaging side," Mr. Smith said.

Attention from the AGA is crucial because the team of engineers wants physicians to help it improve the robot pill, Mr. Luebeke said. "We can build anything, but we need guidance about what the market needs. Doctors have to say, 'We need you to tweak it this way or that way.' "

The business opportunity is large, Mr. Smith said, with 7.5 million upper endoscopies out of 223 million endoscopic procedures done per year in the United States.

Endiatx figures the gross margin on procedures with the robot pills is 90%-95% because the manufacturing cost is about $50 per pill, but physicians can bill $500 for them using existing CPT codes for passive pill cameras.

Dr. Sethi said the robot pill stood out among other contenders because of the dire need for improved endoscopy technology.

Endiatx will represent AGA at the 2023 Digestive Disease Week® (DDW) Shark Tank pitch competition.

Four other finalists

Ezalife's Button Huggie, a device for securing gastrostomy and cecostomy buttons, received the most votes from the audience. The device is a reusable, child-proof lid with a disposable, biodegradable, gauze sponge and a base layer held in place with a long-wearing adhesive. This prevents button movement in the tract, which can delay wound healing and lead to complications. "Our device is novel, with no direct competitors," said CTO/COO Tyler Mironuck.

Currently patients are advised to fasten gastrostomy and cecostomy buttons with tape, but the buttons are dislodged 7% of the time. The company estimates that patients spend an average of $100 a month on tape and gauze. The device can be manufactured for $56, and the company envisions selling them for $300. The device is exempt from needing 510K FDA approval. The company is conducting a clinical trial with 200 patients at five children's hospitals, Mr. Mironuck said.

NovaScan was a finalist for nsCanary, a device that uses electrical impedance to detect cancer. The device hinges on the company's discovery that the Cole relaxation frequency is orders of magnitude different for cancerous and benign tissue, yet not affected by mass. By measuring this frequency, the nsCanary can find cancer in tissue acquired through biopsy forceps, snare polypectomy, mucosal resection, and endoscopic ultrasound-guided fine needle biopsy. It works in seconds without the need to interpret images.

Atlas Endoscopy was recognized for REN, a robotic colonoscopy system. The operator uses an external actuating magnet above the patient to guide a disposable ultracompliant endoscope through the colon. The company says this form of navigation prevents looping, reduces pain, and minimizes tissue stress.

Limaca Medical was recognized for Precision, a motorized, automated, rotational cutting and coring needle for endoscopic ultrasound biopsy. Manual biopsy needles now on the market require repeat passes in and out of the endoscope to obtain fragments of tissue, but Precision obtains larger intact samples of tumor tissue in a single pass.

Dr. Sethi has served as a consultant for Boston Scientific, Medtronic, and Olympus and as a board member for EndoSound. He has received grant support from FUJIFILM. ■

Continued from previous page

patients (6%) in the vedolizumab group and four patients (8%) in the placebo group. One adverse event led to discontinuation of vedolizumab, and no serious adverse events were related to vedolizumab or led to discontinuation of vedolizumab.

'Landmark study'

"This is a landmark study that shows us that a biologic that we have used for Crohn's disease and ulcerative colitis may also be used to treat chronic pouchitis. This is a large unmet need for our patients and an important advancement for the field," said Miguel Regueiro, MD, AGAF, chair of the Digestive Disease and Surgery Institute at the Cleveland Clinic.

The Cleveland Clinic has one of the highest referral rates in the country for IPAA, noted Dr. Regueiro, who wasn't involved with this study. Colleagues are currently conducting studies to determine who may develop pouchitis and understand why certain patients develop pouchitis after the procedure, he said.

One question the EARNEST trial leaves unanswered is whether vedolizumab will be required as a sustained medicine to control pouchitis or could be stopped at some point, he said. "My sense is that, as is the case with any IBD, chronic treatment will be required," he added.

The higher rate of ciprofloxacin use among patients who received vedolizumab is interesting, Dr. Regueiro said.

"[The researchers] note that ciprofloxacin was used for symptoms and do not know if there was active inflammation. It's possible that bacterial overgrowth caused symptoms and the antibiotic treated that, and in a study this small, it is difficult to say anything more," he said.

The study was sponsored by Takeda, the manufacturer of vedolizumab. Several authors reported speaking fees and consultant roles for pharmaceutical companies, including Takeda. Three of the authors are employees of Takeda. Dr. Regueiro reported no relevant disclosures. ■

Patients express need for psychosocial support

BY JIM KLING AND CAROLYN CRIST
MDedge News


Courtesy Joshua Denton

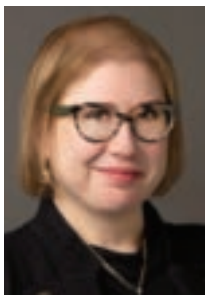
Joshua Denton, who has IBD, serves as a patient advocate for the nonprofit Color of Crohn's & Chronic Illness.

It's been over 2 decades since 37-year-old Joshua Denton was diagnosed with ulcerative colitis.

Controlling the physical symptoms of comorbidities, such as inflammatory bowel disease, have been possible, but he was surprised when depression and anxiety set in.

"You're dealing with what I call the anxiety of the unknown. What does this mean?" said Mr. Denton, who serves as a patient advocate with Color of Crohn's & Chronic Illness, a nonprofit group aimed at improving quality of life for racial-ethnic minorities. "When you understand that it's autoimmune that is chronic and incurable, you're wondering, 'Am I going to have a chance to get better in terms of my quality of life? Is it going to get worse?' It indirectly builds this level of anxiety."

Mr. Denton described a level of anxiety and depression that other patients living with inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, described in a recent survey from the American Gastroenterological Association. Survey results, released in March, show how emotional and social challenges are top of mind for patients living with IBD, but not so much for gastroenterologists who said they're more concerned about treating physical health than emotional health and believe mental health is sufficiently addressed in their patients' IBD care.


Dr. Keefer

In response, the AGA has launched the My IBD Life campaign to provide resources to patients and help their health care providers become active partners in psychosocial care.

Discussions about mental health challenges are difficult for both physician and patients. For patients, they may be unwilling to talk to their physicians out of concern of being a burden, while physicians may be reluctant to pry or intrude. "I want to dispel the myth to the patients (and tell them) that your doctor actually would love to know, but is afraid to pry. And to the doctor: Your patient wants you to know, but is afraid to be a burden," said Laurie A. Keefer, PhD, AGAF, a psychologist at Icahn School of Medicine at Mount Sinai, New York, who specializes in the psychosocial care of patients with chronic digestive diseases and serves as an adviser to the My IBD Life campaign, which was launched to support both patients living with IBD and their health care providers.

But "prying" in this way is important, Dr. Keefer said. Depression and anxiety can have wide-ranging effects on patient outcomes. Depressed patients may not follow through with medication refills or may be more accepting of disability, while anxiety can lead to worries about colonoscopies or surgeries, which can lead to avoidance. "I always tell GI providers, if you can't figure out why someone never follows through with that test or that procedure, consider anxiety before you assume that it's just nonadherence. Anxiety and depression really affect how somebody follows the requirements they need to manage their disease," said Dr. Keefer.

Rates of anxiety among patients are increasing

The survey included 1,026 adults (18-59 years) with IBD, and of these, 63% reported having comorbid conditions, such as anxiety (36%) and depression (35%). These rates are significantly higher than in the general population – at 19% and 8%, respectively. The rate of anxiety among patients with IBD has increased since AGA conducted a similar survey in 2017.

Patients reported that they were most concerned with the ways that IBD affects their mental health or emotional health and day-to-day life. Many said their providers were more concerned about treating them physically than emotionally and expressed a need for additional information on IBD treatment options (37%) and medications (35%). They also desired more information about the impact on emotional and mental health (25%), which has increased since the 2017 survey.

The No. 1 concern for patients was the need to consider bathroom logistics when away from home (7.03 on a scale of 1-10). The second most popular concern was mental and emotional health with a rating of 6.51 on a 1-10 scale. Thirty percent requested more information about diet, and 27% asked for more information about general IBD symptoms.

Both patients and providers were less satisfied with emotional and social care than physical care for IBD. Among patients, women and those between ages 18 and 39 said they were the least satisfied with their care.

"We must always consider the mind and body together when managing a chronic disease, and IBD is no exception," Dr. Keefer said. "We also know that failure to address emotional concerns in IBD leads to poorer disease outcomes, not just reduced quality of life."

The surveys also highlighted different experiences among communities. For instance, people of color, particularly those in the Black community, were more likely to report that their IBD journey was impacted by their personal identity, whether by race, ethnicity, culture, sexual orientation, gender identity, or age.

In contrast, a companion survey of 117 gastroenterologists found that providers are focused on physical health over emotional health (8.34 on a scale of 1-10), but they reported having sufficiently addressed concerns their patients may have expressed about mental health issues. At the same time, many also said they feel more equipped to treat their patients physically rather than emotionally.

The provider survey showed their biggest challenge was in securing insurance authorizations for medications.

Mr. Denton encourages all patients to be as transparent as possible with their providers and family members.

"I firmly believe you cannot internalize the experience and keep it to yourself. I strongly encourage other patients with IBD to continue to push themselves to be as transparent as possible with their loved ones and health care professionals. The more we talk about it, the more we can humanize the experience and allow people that aren't healthcare professionals to have a more empathetic understanding of what we're dealing with which, in turn, hopefully, will provide better support and resources," Mr. Denton said.

The My IBD Life website (www.MyIBDLife.org) provides resources for patients to navigate a range of common scenarios, including conversations about new medications, workplace concerns, intimacy and relationships, vacations and travel, and medical procedures and surgeries. An interactive 3D graphic demonstrates how IBD affects the body, and videos of patients highlight personal experiences and ways to build emotional resilience.

The My IBD Life campaign is supported by an independent grant from Bristol Myers Squibb.

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Approach to dysphagia

BY TANISHA RONNIE, MD; LAUREN BLOOMBERG, MD; AND MUKUND VENU, MD, FACG

Dr. Ronnie and **Dr. Bloomberg** are in the department of internal medicine at Loyola University Chicago, Maywood, Ill. **Dr. Venu** is in the division of gastroenterology at Loyola. He is on the speakers bureau at Medtronic.

Introduction

Dysphagia is the sensation of difficulty swallowing food or liquid in the acute or chronic setting. The prevalence of dysphagia ranges based on the type and etiology but may impact up to one in six adults.[1,2] Dysphagia can cause a significant impact on a patient's health and overall quality of life. A recent study found that only 50% of symptomatic adults seek medical care despite modifying their eating habits by either eating slowly or changing to softer foods or liquids.[1] The most common, serious complications of dysphagia include aspiration pneumonia, malnutrition, and dehydration.[3] According to the Agency for Healthcare Research and Quality, dysphagia may be responsible for up to 60,000 deaths annually.[3]

The diagnosis of esophageal dysphagia can be challenging. An initial, thorough history is essential to delineate between oropharyngeal and esophageal dysphagia and guide subsequent diagnostic testing. In recent years, there have been a number of advances in the approach to diagnosing dysphagia, including novel diagnostic modalities. The goal of this review article is to discuss the current approach to esophageal dysphagia and future direction to allow for timely diagnosis and management.

History

The diagnosis of dysphagia begins with a thorough history. Questions about the timing, onset, progression, localization of symptoms, and types of food that are difficult to swallow are essential in differentiating oropharyngeal and esophageal dysphagia.[3,4] Further history taking must include medication and allergy review, smoking history, and review of prior radiation or surgical therapies to the head and neck.

Briefly, oropharyngeal dysphagia is difficulty initiating a swallow or passing food from the mouth or throat and can be caused by structural or functional etiologies.[5] Clinical presentations include a sensation of food stuck in the back of the throat, coughing or choking while eating, or drooling. Structural causes include head and neck cancer, Zenker diverticulum, Killian Jamieson diverticula, prolonged intubation, or changes secondary to prior surgery or radiation.[3] Functional causes may include neurologic, rheumatologic, or muscular disorders.[6]

Esophageal dysphagia refers to difficulty transporting food or liquid down the esophagus and can be caused by structural, inflammatory, or functional disorders.[5]

A recent study found that only 50% of symptomatic adults seek medical care despite modifying their eating habits by either eating slowly or changing to softer foods or liquids.

Patients typically localize symptoms of heartburn, regurgitation, nausea, vomiting, cough, or chest pain along the sternum or epigastric region. Alarm signs concerning for malignancy include unintentional weight loss, fevers, or night sweats.[3,7] Aside from symptoms, medication review is essential, as dysphagia is a common side effect of antipsychotics, anticholinergics, antimuscarinics, narcotics, and immunosuppressant drugs.[8] Larger pills such as NSAIDs, antibiotics, bisphosphonates, potassium supplements, and methylxanthines can cause drug-induced esophagitis, which can initially present as dysphagia.[8] Inflammatory causes can be elucidated by obtaining a history about allergies, tobacco use, and recent infections such as thrush or pneumonia. Patients with a history of recurrent pneumonias may be silently aspirating, a complication of dysphagia.[3] Once esophageal dysphagia is clinically suspected based on history, workup can begin.

Differentiating etiologies of esophageal dysphagia

The next step in diagnosing esophageal dysphagia is differentiating between structural, inflammatory, or dysmotility etiology (figure on next page).

Patients with a structural cause typically have difficulty swallowing solids but are able to swallow liquids unless the disease progresses. Symptoms can rapidly worsen and lead to odynophagia, weight loss, and vomiting. In comparison, patients with motility disorders typically have difficulty swallowing both solids and liquids initially, and symptoms can be constant or intermittent.[5]

Prior to diagnostic studies, a 4-week trial of a proton pump inhibitor (PPI) is appropriate for patients with reflux symptoms who are younger than 50 with no alarm features concerning for malignancy.[7,9] If symptoms persist after a PPI trial, then an upper endoscopy (EGD) is indicated. An EGD allows for visualization of structural etiologies, obtaining biopsies to rule out inflammatory etiologies, and the option to therapeutically treat reduced luminal diameter with dilatation.[10] The most common structural and inflammatory etiologies noted on EGD include strictures, webs, carcinomas, Schatzki rings, and gastroesophageal reflux or eosinophilic esophagitis.[4]

If upper endoscopy is normal and clinical suspicion for an obstructive cause remains high, barium esophagram can be utilized as an adjunctive study. Previously, barium esophagram was the initial test to distinguish between structural and motility disorders. The benefits of endoscopy over barium esophagram as the first diagnostic study include higher diagnostic yield, higher sensitivity and specificity, and lower costs.[7] However, barium studies may be more sensitive for lower esophageal rings or extrinsic esophageal compression.[3]

Evaluation of esophageal motility disorder

If a structural or inflammatory etiology of dysphagia is not

Dysphagia is a common gastrointestinal complaint in the outpatient setting but difficult to tackle, as the symptom may be nonspecific and etiologies can be numerous. Particularly among young gastroenterologists, approaching a patient with dysphagia may be overwhelming.

In this issue's In Focus, Dr. Tanisha Ronnie, Dr. Lauren Bloomberg, and Dr. Mukund Venu develop a systematic approach to investigating the cause of dysphagia. They emphasize the importance of a detailed history and the role of various diagnostic tests.

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

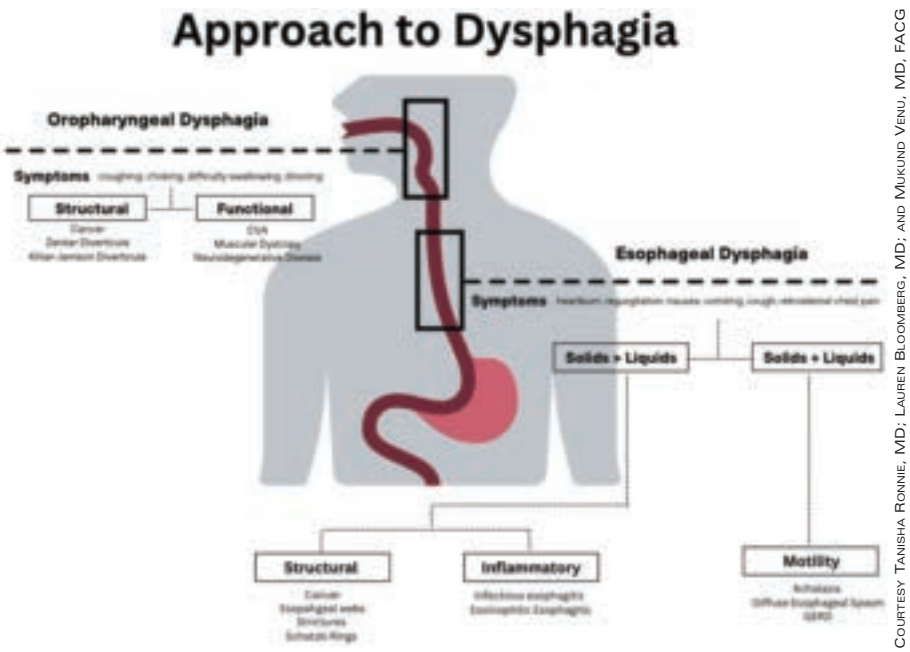
identified, investigation for an esophageal motility disorder (EMD) is warranted. Examples of motility disorders include achalasia, ineffective esophageal motility, hypercontractility, spasticity, or esophagogastric junction outflow obstruction (EGJOO).[10,11] High-resolution esophageal manometry (HRM) remains the gold standard in diagnosis of EMD.[12] An HRM catheter utilizes 36 sensors placed 2 centimeters apart and is placed in the esophagus to evaluate pressure and peristalsis between the upper and lower esophageal sphincters.[13] In 2009, the Chicago Classification System was developed to provide a diagnostic algorithm that categorizes EMD based on HRM testing, with the most recent version (4.0) being published in 2020.[12,14] Motility diagnoses are divided into two general classifications of disorders of body peristalsis and disorders of EGJ outflow. The most recent updates also include changes in swallow protocols, patient positioning, targeted symptoms, addition of impedance sensors, and consideration of supplemental testing when HRM is inconclusive based on the clinical context.[12] There are some limitations of HRM to highlight. One of the main diagnostic values used with HRM is the integrated relaxation pressure (IRP). Despite standardization, IRP measurements vary based on the recorder and patient position. A minority of patients with achalasia may have IRP that does not approach the accepted cutoff and, therefore, the EGJ is not accurately assessed on HRM.[15,16] Some swallow protocols have lower sensitivity and specificity for certain motility disorders, and the test can result as inconclusive.[14] In these scenarios, supplemental testing with timed barium esophagram or functional luminal imaging probe (EndoFLIP) is indicated.[10,11]

Over the past decade, EndoFLIP has emerged as a novel diagnostic tool in evaluating EMD. EndoFLIP is usually completed during an upper endoscopy.

EndoFLIP has emerged as a novel diagnostic tool in evaluating EMD over the past decade. EndoFLIP is usually completed during an upper endoscopy and utilizes impedance planimetry to measure cross-sectional area and esophageal distensibility and evaluate contractile patterns.[16] During the procedure, a small catheter with an inflatable balloon is inserted into the esophagus with the distal end in the stomach, traversing the esophagogastric junction (EGJ). The pressure transducer has electrodes every centimeter to allow for a three-dimensional construction of the esophagus and EGJ.[17] EndoFLIP has been shown to accurately measure pyloric diameter, pressure, and distensibility at certain balloon volumes.[18] In addition, FLIP is being used to further identify aspects of esophageal dysmotility in patients with eosinophilic esophagitis, thought primarily to be an inflammatory disorder.[19] Limitations include minimal accessibility of EndoFLIP within clinical practice and a specific computer program needed to generate the topographic plots.[20]

When used in conjunction with HRM, EndoFLIP provides complementary data that can be used to better detect major motility disorders.[15,20,21] Each study adds unique information about the different physiologic events comprising the esophageal response to distention. Overall, the benefits of EndoFLIP include expediting workup during index endoscopy, patient comfort with sedation, and real-time diagnostic data that supplement results obtained during HRM.[10,16,20,22,23]

If the diagnostic evaluation for structural, inflammatory, and motility disorders are unrevealing, investigating for atypical reflux symptoms can be pursued for patients with persistent dysphagia. Studies investigating pH, or acidity in the esophagus, in relation to symptoms, can be conducted wirelessly via a capsule fixed to the mucosa or with a nasal catheter.[3]



Courtesy Tanisha Ronnie, MD; Lauren Bloomberg, MD; and Mukund Venu, MD, FACG

Normal workup – hypervigilance

In a subset of patients, all diagnostic testing for structural, inflammatory, or motility disorders is normal. These patients are classified as having a functional esophageal disorder. Despite normal testing, patients still have significant symptoms including epigastric pain, chest pain, globus sensation, or difficulty swallowing. It is theorized that a degree of visceral hypersensitivity between the brain-gut axis contributes to ongoing symptoms.[24] Studies for effective treatments are ongoing but typically include cognitive-behavioral therapy, brain-gut behavioral therapy, swallow therapy, antidepressants, or short courses of PPIs.[9]

Conclusion

In this review article, we discussed the diagnostic approach for esophageal dysphagia. Initial assessment requires a thorough history, differentiation between oropharyngeal and esophageal dysphagia, and determination of who warrants an upper endoscopy. Upper endoscopy may reveal structural or inflammatory causes of dysphagia, including strictures, masses, or esophagitis, to name a few. If a structural or inflammatory cause is ruled out, this warrants investigation for esophageal motility disorders. The current gold standard for diagnosing EMD is manometry, and supplemental studies, including EndoFLIP, barium esophagram, and pH studies, may provide complimentary data. If workup for dysphagia is normal, evaluation for esophageal hypervigilance causing increased sensitivity to normal or mild sensations may be warranted. In conclusion, the diagnosis of dysphagia is challenging and requires investigation with a systematic approach to ensure timely diagnosis and treatment. ■

References

1. Adkins C et al. Clin Gastroenterol Hepatol. 2020;18(9):1970-9.e2.
2. Bhattacharyya N. Otolaryngol Head Neck Surg. 2014;151(5):765-9.
3. McCarty EB and Chao TN. Med Clin North Am. 2021;105(5):939-54.
4. Thiyagalingam S et al. Mayo Clin Proc. 2021;96(2):488-97.
5. Malagelada JR et al. J Clin Gastroenterol. 2015;49(5):370-8.
6. Rommel, N and Hamdy S. Nat Rev Gastroenterol Hepatol. 2016;13(1):49-59.
7. Liu LWC et al. J Can Assoc Gastroenterol. 2018;1(1):5-19.
8. Schwemmle C et al. HNO. 2015;63(7):504-10.
9. Moayyedi P et al. Am J Gastroenterol. 2017;112(7):988-1013.
10. Triggs J and Pandolfino J. F1000Res. 2019 Aug 29. doi: 10.12688/f1000research.18900.1.
11. Yadlapati R et al. Neurogastroenterol Motil. 2021;33(1):e14058.
12. Yadlapati R et al. Neurogastroenterol Motil. 2021;33(1):e14053.
13. Fox M et al. Neurogastroenterol Motil. 2004;16(5):533-42.
14. Sweis R and Fox M. Curr Gastroenterol Rep. 2020;22(10):49.
15. Carlson DA et al. Gastroenterology. 2015;149(7):1742-51.
16. Donnan EN and Pandolfino JE. Gastroenterol Clin North Am. 2020;49(3):427-35.
17. Carlson DA. Curr Opin Gastroenterol. 2016;32(4):310-8.
18. Zheng T et al. Neurogastroenterol Motil. 2022;34(10):e14386.
19. Carlson DA et al. Clin Gastroenterol Hepatol. 2022;20(8):1719-28.e3.
20. Carlson DA et al. Am J Gastroenterol. 2016;111(12):1726-35.
21. Carlson DA et al. Neurogastroenterol Motil. 2021;33(10):e14116.
22. Carlson DA et al. Gastrointest Endosc. 2019;90(6):915-23.e1
23. Fox MR et al. Neurogastroenterol Motil. 2021;33(4):e14120.
24. Aziz Q et al. Gastroenterology. 2016 Feb 15. doi: 10.1053/j.gastro.2016.02.012.

Protect the next generation of GI investigators

Investing in research is the only way we will identify new diagnostics and treatments.

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Donate today to help protect the GI research pipeline. Make a tax-deductible donation at www.foundation.gastro.org. ■

AGA guidelines, CPUs lead education at DDW® 2023

Get the latest recommendations for treating your patients at Digestive Disease Week® (DDW) 2023.

Below is a sampling of AGA's invited speaker sessions we're excited about this year for clinical practitioners.

To view other AGA program highlights, check out the DDW Preliminary Program.

- Guidelines Highlights 2023
- Clinical Practice Updates: Battle of the Heavyweights
- AGA Clinical Symposium
- Case Studies in Measuring Care and Improving Quality
- Optimizing Your GI Practice: Guidelines, Quality and Delivery
- AGA Postgraduate Course ($)
- Surviving the First Years in Clinical Practice: Roundtable With the Experts
- Register: https://rb.gy/6sjw2 ■

Reforming prior authorization remains AGA's top policy priority

BY AGA GOVERNMENT AFFAIRS COMMITTEE

Reforming prior authorization polices to reduce red tape for physicians and help patients get the care they need in a timely manner is the AGA's No. 1 policy priority as it impacts every gastroenterologist regardless of practice setting. We have seen an increase in prior authorization policies from every major insurer. The most recent prior authorization program to impact gastroenterologists was announced by UnitedHealthcare (UHC) in March for implementation on June 1 and will require prior authorization for most colonoscopy and upper GI endoscopy procedures with the exception of screening colonoscopy.[1] This policy is a step back at a time when payers should be developing innovative policies in collaboration with healthcare providers to improve patient care.

UHC's GI prior authorization policy

AGA met with UHC in March to discuss their plan to require prior authorization for most GI endoscopy procedures. We stressed how this change will cause care delays for high-risk individuals, deter patients from undergoing medically recommended procedures, exacerbate existing sociodemographic disparities in care and outcomes, and add unnecessary paperwork burden to physicians who have mounting rates of burnout.

Linda A. Lee, MD, AGAF, medical director of endoscopy at Brigham and Women's Hospital, Boston, recently spoke of the impact this policy will have on gastroenterologists and their patients. "We all know that requiring prior authorizations really only leads to more bureaucracy within the insurance company, as well as within each health care provider's practice, because we need people to fill out these prior authorization forms, waste time trying to get through to their 1-800 number to speak with someone who has no clinical knowledge, then be told we need to speak with someone else who actually does have some medical knowledge about why these procedures are necessary."

However, Dr. Lee stressed that "most importantly, this will lead to poorer patient care with delays in care as we are struggling to wade through the morass of prior authorization while patients are bleeding, not able to swallow, vomiting, and more while waiting for their insurance company to approve their potentially life-saving procedures."

We were particularly troubled that UHC announced this policy during Colorectal Cancer Awareness Month, given the need to screen more Americans for colorectal cancer which remains the nation's No. 2 cancer killer. The UHC program would require a PA on surveillance colonoscopy for those patients who have previously had polyps removed and are at a higher risk for developing colorectal cancer.

Continued on following page

Member SPOTLIGHT

Taking a global leap into GI technology

BY JENNIFER LUBELL
MDedge News

Sharmila Anandasabapathy, MD, AGAF, knew she wanted to focus on endoscopy when she first started her career. Her passion would someday translate into a worldwide effort to expand and test this technology.

While leading an endoscopy unit in New York City, Dr. Anandasabapathy began developing endoscopic and imaging technologies for underresourced and underserved areas. These technologies eventually made their way into global clinical trials.

"We've gone to clinical trial in over 2,000 patients worldwide. When I made that jump into global GI, I was able to make that jump into global health in general," said Dr. Anandasabapathy.

As vice president for global programs at Baylor College of Medicine in Houston, Dr. Anandasabapathy currently focuses on clinical and translational research.

"We're looking at the development of new, low-cost devices for early cancer detection in GI globally. I oversee our global programs across the whole college, so it's GI, it's surgery, it's anesthesia, it's obstetrics, it's everything."

In an interview, Dr. Anandasabapathy discussed what attracted her to gastroenterology and why she always takes the time to smile at her patients.


Baylor College of Medicine

Dr. Sharmila Anandasabapathy

Q: Why did you choose GI?
A: There's two questions in there: Why I chose GI and why I chose endoscopy.

I chose GI because when I was in my internal medicine training, they seemed like the happiest people in the hospital. They liked what they did. You could make a meaningful impact even at 3 a.m. if you were coming in for a variceal bleed. Everybody seemed happy with their choice of specialty. I was ready to be an oncologist, and I ended up becoming a gastroenterologist.

I chose endoscopy because it was where I wanted to be when I woke up in the morning. I was happy there. I love the procedures; I love the hand-eye coordination. I liked the fact that these were relatively shorter procedures, that it was technology based, and there was infinite growth.

Q: Was there a time when you really helped a patient by doing that endoscopy, preventing Barrett's esophagus or even cancer?
A: I can think of several times where we had early cancers and it was a question between endoscopic treatment or surgery. It was always discussed with the surgeons. We made the decision within a multidisciplinary group and with the patient, but we usually went with the endoscopic options and the patients have done great. We've given them a greater quality of life, and I think that's really rewarding.

Q: What gives you the most joy in your day-to-day practice?
A: My patients. I work with Barrett's esophagus patients, and they tend to be well informed about the research and the science. I'm lucky to have a patient population that is really interested and willing to participate in that. I also like my students, my junior faculty. I like teaching and the global application of teaching.

Q: What fears did you have to push past to get to where you are in your career?
A: That I would never become an independent researcher and do it alone. I was able to, over

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"We know that patients with high-risk adenomas or advanced sessile serrated lesions have a higher risk of developing colorectal cancer, and timely access to the necessary surveillance colonoscopy is critical," said David Lieberman, MD, AGAF, past president of the AGA and chair of the AGA Executive Committee on the Screening Continuum.

AGA plans to meet with UHC again to ask them to reconsider this policy, but we need your advocacy now to tell United how this will impact you and your patients.

How you can help stop UHC's prior authorization program

Write to UHC: Tell UHC how this policy would impact you and your patients. Contact their CEO using our customizable letter[2] that outlines the impact of United's GI endoscopy prior authorization program on gastroenterologists and their patients available on the AGA Advocacy Action Center.

Use social media: Tag United (@UHC) on Twitter and tell them how this burdensome program will cause delays for high-risk individuals, deter patients from seeking treatment, and exacerbate existing disparities in care, all while saddling physicians with even more paperwork. Once you've tweeted, tag your colleagues and encourage them to get involved.

AGA is working to reform prior authorization

The AGA has supported federal legislation that would streamline prior authorization processes in Medicare Advantage (MA), the private insurance plans that contract with the Medicare program, given the explosion of these policies over the past several years. The Improving Seniors Timely Access to Care Act, bipartisan, bicameral legislation, would reduce prior authorization burdens by:

- Establishing an electronic prior authorization (ePA) program and require MA plans to adopt ePA capabilities.
- Requiring the Secretary of Health & Human Services to establish a list of items and services eligible for real-time decisions under an MA ePA program.
- Standardizing and streamlining the prior authorization process for routinely approved items and services.
- Ensuring prior authorization requests are reviewed by qualified medical personnel.
- Increasing transparency around MA prior authorization requirements and their use.
- Protecting beneficiaries from any disruptions in care due to prior authorization requirements as they transition between MA plans.

The Centers for Medicare & Medicaid Services has also recognized the impact that prior authorization is having on physician wellness and how it is contributing to physician burnout. The agency recently proposed implementing many of the provisions that are outlined in the legislation, and AGA has expressed our support for moving forward with many of their proposals.

Earlier this year, Shivan Mehta, MD, MPH, met with CMS administrator Chiquita Brooks-LaSure and Surgeon General Vivek Murthy, MD, MBA, to express AGA's support for prior authorization reform and discussed how it impacts how patients with chronic conditions like inflammatory bowel disease maintain continuity of care. He also stressed how prior authorization further exacerbates health inequities since it creates an additional barrier to care when barriers already exist.

AGA is taking a multi-pronged approach to advocating for prior authorization reform and reducing paperwork through legislative advocacy, regulatory advocacy with the CMS, and payer advocacy. We can't do this alone. Join our AGA Advocacy Center[3] and get involved in our AGA Congressional Advocates Program.[4]

The authors have no conflicts to declare. ■

References

1. UnitedHealthcare (2023 Mar 01) New requirements for gastroenterology services.

2. American Gastroenterological Association (n.d.) AGA Advocacy Action Center. Tell United to Stop New Prior Auth Requirements!

3. American Gastroenterological Association (n.d.) AGA Advocacy Action Center. Advocacy & Policy. Get Involved.

4. American Gastroenterological Association (n.d.) AGA Congressional Advocates Program.

Antibiotic pretreatment reduces liver ischemia/reperfusion injury

BY CAROLYN CRIST
MDedge News

Antibiotic pretreatment may protect against liver ischemia/reperfusion (I/R) injury through altered gut microbiota, glutamine levels, and glutamine downstream products in circulation, according to a recent study in Cellular and Molecular Gastroenterology and Hepatology.

The findings show that gut microbiota and their metabolites play critical roles in hepatic I/R injury by modulating macrophage metabolic reprogramming, wrote Tianfei Lu, with the Abdominal Transplant Surgery Center at Ruijin Hospital and Shanghai (China) Jiao Tong University, and colleagues.

"Potential therapies that target macrophage metabolism, including antibiotic therapies and novel immunometabolism modulators, can be exploited for the treatment of liver I/R injury," the authors wrote (Cell Mol Gastroenterol Hepatol. 2023 Jan 24. doi: 10.1016/j.jcmgh.2023.01.004).

Liver I/R injury is a common complication of liver resection, transplantation, trauma, and hemorrhagic shock. Previous studies have noted the important role of gut microbiota in liver disease progression, yet the mechanisms in liver I/R injury remain unknown.

The researchers pretreated mice with an antibiotic cocktail to modify the gut microbiome. They found that the pretreatment showed protective effects against hepatic I/R injury, with reductions in serum alanine aminotransferase (ALT), interleukin-1 beta, tumor necrosis factor–alpha, IL-6, IL-12b, and CXCL10.

Through histologic analysis of liver tissues, they also found that the area of necrosis, the degree of congestion and edema, and the presence of vacuole-like lesions were alleviated in the preconditioned mice. Inflammation and necrosis of the liver were also lower, according to both qualitative and quantitative data.

Then, through fecal microbiota transplantation into germ-free mice, they found that the protection from I/R injury was transferable. This finding indicated that the altered gut microbiome, rather than the antibiotic treatment itself, exerted the protective effect.

Because altered gut microbiota can cause changes in metabolites, the researchers used ultra-performance liquid chromatography coupled to tandem mass spectrometry to explore the changes of gut microbiota and metabolites in both feces and portal blood, as well as analyze the mechanisms underlying their protective effects in liver I/R injury.

The researchers found that glutamine and its downstream product called alpha-ketoglutarate (AKG) were present in higher concentrations in feces and blood in the mice with antibiotic pretreatment. Glutamate levels were significantly lower, indicating that glutamine is converted into AKG through glutamate after entering the blood.

In addition, there were increased levels of intermediate products of the tricarboxylic acid (TCA) cycle, as well as pyruvate produced by glycolysis. That led to an increase in M2 macrophages, which are responsible for anti-inflammatory processes and tissue repair.

The authors concluded that

Continued on following page

In modern clinical practice, multiple conditions can cause ischemia and reperfusion injury to the liver, including surgical liver resection, liver transplantation, and physical trauma to the organ. Liver damage due to hypoxia is followed by reperfusion injury, resulting in a pre-proinflammatory environment. Liver resident macrophages called Kupffer cells are major mediators of this response, initiating a signaling cascade that leads to recruitment of neutrophils, natural killer cells, and circulating macrophages, which attack sinusoidal endothelial cells and hepatocytes.


Dr. Kaestner

In the current issue of CMGH, Lu and colleagues address the question of to what extent do the gut microbiome and its metabolite products, which reach the liver via the portal circulation, play a role in the severity of ischemia and reperfusion injury (Cell Mol Gastroenterol Hepatol. 2023 Jan 24. doi: 10.1016/j.jcmgh.2023.01.004). This topic is of clinical relevance, as the microbial load of the gut lumen can be easily reduced by several orders of magnitude using non-absorbed antibiotics. Thus, it is important to establish if pretreatment of patients scheduled for liver resection or transplantation might benefit from preprocedure antibiotic treatment.

Remarkably, Lu and colleagues find that antibiotic preconditioning significantly reduces ischemia and reperfusion injury in an animal model. Mechanistically, they linked the protective effects to a shift of macrophage polarization to the protective M phenotype, which is known to promote tissue repair. These findings suggest that the antibiotic preconditioning of patients who are undergoing procedures with significant ischemia and reperfusion injury should be evaluated in future clinical trials.

Klaus H. Kaestner, PhD, MS, is the Thomas and Evelyn Suor Butterworth Professor in Genetics and associate director of the Penn Diabetes Research Center at the University of Pennsylvania, Philadelphia. He has no relevant financial relationships.

Continued from previous page

time. The ability to transition from being independent to teaching others and making them independent is a wonderful one.

Early on when I was doing GI, I remember looking at my division, and there were about 58 gastroenterologists and only 2 women. I thought at the time, "Well, can I do it? Is this a field that is conducive with being a woman and having a family?" It turned out that it is. Today, I'm really gratified to see that there are more women in GI than there ever were before.

Q: Have you ever received advice that you've ignored?

A: Yes. Early in my training in internal medicine, I was told that I smiled too much and that my personality was such that patients and others would think I was too glib. Medicine was a serious business, and you shouldn't be smiling. That's not my personality – I'm not Eeyore. I think it's served me well to be positive, and it's served me well with patients to be smiling. Especially when you're dealing with patients who have precancer or dysplasia and are scared – they want reassurance and they want a level of confidence. I'm glad I ignored that advice.

Q: What would be your advice to medical students?

A: Think about where you want to be when you wake up in the morning. If it's either in a GI practice or doing GI research or doing endoscopy, then you should absolutely do it. ■

Dr. Anandasabapathy is on LinkedIn at https://www.linkedin.com/in/sharmila-anandasabapathy-24816362 and on Twitter at @anandasabapathy, @bcmglobalhealth, and @bcm_gihep.

Lightning round

Cat person or dog person?
Dog

Favorite sport?
Tennis

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

Favorite music genre?
1980s pop

Favorite movie, show, or book?
Wuthering Heights

AGA Clinical Practice Update: Expert Review

Alpha-gal syndrome often causes GI issues

BY WILL PASS
MDedge News

Alpha-gal syndrome is an increasingly common cause of gastrointestinal issues that remains underrecognized by the medical community, according to an American Gastroenterological Association clinical practice update.

Although the allergic response is best known for a combination of anaphylaxis, skin changes, and gastrointestinal symptoms that occurs within hours of consuming mammalian-derived food products, health care providers should know that many patients experience gastrointestinal distress in the absence of other clinical signs, lead author Sarah K. McGill, MD, MSc, AGAF, of the University of North Carolina at Chapel Hill, and colleagues reported.

"It is important for gastroenterologists to be aware of this condition and to be capable of diagnosing and treating it in a timely manner," the investigators wrote in Clinical Gastroenterology and Hepatology (2023 Feb 24. doi: 10.1016/j.cgh.2022.12.035).

The clinical practice update covers pathogenesis, clinical manifestations, diagnosis, and management.

"The allergy in alpha-gal syndrome is to galactose alpha-1,3-galactose, an oligosaccharide on the cells of all nonprimate mammals," the investigators wrote. "Surprisingly, sensitization to alpha-gal, that is, the process by which human beings develop IgE antibodies to the sugar, is understood to occur after the bite of a tick or parasitic infection. In the United States, the Lone Star tick, an ectoparasite whose principal host is deer, is strongly implicated."


Dr. McGill

Gastrointestinal focused clinical research is scarce, the investigators noted, citing two observational studies involving 375 patients positive for alpha-gal IgE. Almost half of these patients (40.7%) had gastrointestinal symptoms alone. Across the entire population, the most common gastrointestinal symptoms were abdominal pain (71%) and vomiting (22%). About three out of four patients reported improvement on an alpha-gal avoidance diet.

"Clinicians should consider alpha-gal syndrome in the differential diagnosis of patients with unexplained gastrointestinal symptoms of abdominal pain, diarrhea, nausea, and vomiting, particularly those who live or have lived in an alpha-gal–prevalent area," the investigators wrote.

In the United States, these areas span the domain of the Lone Star tick, including most of the East Coast, the central Midwest, the South, and all of Texas. Overseas, alpha-gal syndrome has been reported in Japan, Australia, Western Europe, and South Africa. Clinical suspicion should be increased in patients with a history of tick bite, engagement in outdoor activities, and awakening in the night with gastrointestinal distress (because of the delay between allergen ingestion and symptom onset). Workup should include serum testing for alpha-gal IgE antibodies. Serum positivity alone is not sufficient for diagnosis. It must be confirmed by symptom resolution or improvement upon adherence to an alpha-gal avoidance diet for at least a month.

"During this time, patients may want to avoid eating at restaurants, which can easily cross-contaminate food, and processed food, which may contain alpha-gal in additives," the authors wrote. Patients with alpha-gal syndrome who accidentally consume alpha-gal should take 25-50 mg of diphenhydramine and have access to epinephrine if symptoms progress, particularly if respiratory compromise occurs.

Coauthors include Jana G. Hasash, MD, and Thomas A. Platts-Mills, MD, PhD. Authors disclosed relationships with Olympus America, Exact Sciences, Guardant Health, Finch Therapeutics, and others. ■

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elevated glutamine levels in the intestine cause an increase in AKG levels in the blood, and AKG can promote M2 macrophage polarization by fueling the TCA cycle. In turn, the increased number of M2 macrophages can repair hepatic I/R injury.

Finally, the researchers tested oligomycin A, which can block the OXPHOS metabolic pathway and inhibit the mitochondrial ATP synthase. As expected, they wrote, the protective effect of antibiotic pretreatment reversed, M2 macrophages decreased, and serum ALT levels increased.

"The immunometabolism and polarization of macrophages play an important role in host homeostasis and the development of various diseases," the authors wrote. "The relationship between antibiotics treatment, altered gut microbiota, and liver I/R injury are complex and worthy of further study."

The study was supported by the China National Science and Technology Major Project, National Natural Science Foundation of China, and Natural Science Foundation exploration project of Zhejiang province. The authors disclosed no conflicts. ■

TMEM16A, TMEM16F play crucial role in Paneth cell secretion

BY CAROLYN CRIST
MDedge News

To defend the gut from microbes and pathogens, Paneth cells rely on TMEM16A, a calcium-activated chloride channel, and TMEM16F, a phospholipid scramblase, according to a new study published in Gastro Hep Advances (2022 Aug 7. doi: 10.1016/j.gastha.2022.08.002).

The Paneth cells in mice missing TMEM16A or TMEM16F showed defects in signaling and release of secretary factors, researchers reported.

Inhibiting or activating TMEM16A and TMEM16F is likely to affect microbial content and immune functions in the small intestine, wrote authors who were led by Karl Kunzelmann, MD, University of Regensburg, Germany.

"Many small molecules and numerous natural or herbal compounds have been identified that either inhibit or activate TMEM16A or TMEM16F," they wrote. "Some of these compounds may turn out to be useful therapeutics in inflammatory bowel disease, intestinal allergies, or abnormal colonization of the gut."

Paneth cells play a central role in intestinal innate immune response, the authors wrote. Located at the base of small intestinal crypts and occasionally found in the proximal colon, these cells have defensive functions, such as protecting stem cells in response to invading microbes and eradicating ingested pathogens from intestinal crypts. Through secretion, they also regulate the composition and number of commensal intestinal bacteria. In inflammatory bowel disease, the Paneth cell zone expands due to an increase in cell size and cell number.

In previous studies, cholinergic stimulation provided enhanced protection in animals orally infected with virulent *Salmonella enterica*. However, the mechanisms of luminal stimulation of Paneth cell secretion in response to bacteria or lipopolysaccharide are unclear. Recent reports show that TMEM16A (also known as anoctamin 1, or ANO1) and TMEM16F (anoctamin 6, or ANO6) control intracellular calcium (Ca2+) signaling and that high local Ca2+ levels support exocytosis in intestinal cells.

Researchers analyzed the roles of the 2 molecules in Paneth cell secretion using mice with intestinal epithelial-specific knockout of TMEM16A or TMEM16F. They examined tissue structures and Paneth cells in the mice, as well as Paneth cell exocytosis in small intestinal organoids in vitro. They also compared Ca2+ signals between wild-type and knockout mice and analyzed bacterial colonization and intestinal apoptosis.

In wild-type mice, TMEM16A was detected at the apical pole of crypt epithelial cells, while

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Refined incidence rate of HCC with alcohol-associated cirrhosis encourages surveillance

BY WILL PASS
MDedge News

Hepatocellular carcinoma (HCC) is relatively common among patients with alcohol-associated cirrhosis, reaching a cumulative incidence of 9% at the 10-year mark, shows a large pooled analysis.

Incidence rates were higher for cohorts that underwent HCC surveillance versus those that did not undergo surveillance, suggesting that such programs offer significant benefit, lead author Daniel Q. Huang, MBBS, of the University of California San Diego, and colleagues reported.

"A systematic review of the incidence of HCC among patients with alcohol-associated cirrhosis has not been reported," the investigators wrote in Clinical Gastroenterology and Hepatology (2022 Aug 4. doi:

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The association between cirrhosis and hepatocellular carcinoma risk is well known and therefore routine surveillance is recommended by the American Association for the Study of Liver Diseases. More recent data have shown alcohol use to be an independent risk factor for HCC along with various other cancers.

In this systematic review and meta-analysis by Huang and colleagues, the incidence of HCC in those with alcohol-associated cirrhosis at 1, 5, and 10 years was 1%, 3%, and 9%, respectively. Interestingly, this study found lower rates of hepatocellular carcinoma in those patients with cirrhosis related to alcohol as compared with nonalcoholic fatty liver disease (NAFLD) and hepatitis C. These findings may, however, be caused by an underestimate of HCC as those enrolled in a surveillance program had higher rates of HCC (18.6 vs. 4.8 per 1,000 person-years; $P = .001$).

Quite frequently, the focus of management in patients with alcohol-associated liver disease is alcohol cessation to prevent further decompensation, with screening often being overlooked. Previous studies have shown, however, that earlier detection is associated with improved survival. Another interesting finding of this study was that those patients who had concomitant smoking use, diabetes, and hepatic decompensation were more likely to develop HCC. When managing patients with alcohol-related liver disease, confounding risk factors should be mitigated (that is, encouragement of smoking cessation, enhanced screening for diabetes, and more rigorous screening in decompensated patients).


Dr. Maddur

This study brings to light the need for improved screening and concomitant risk factor mitigation for hepatocellular carcinoma given higher rates of detection in those undergoing surveillance. Larger, prospective studies are needed, however, to validate the findings in this study given the recent overall increase in rates of alcohol-associated liver disease.

Priya Maddur MD, is a visiting clinical associate professor of medicine, University of Arizona, Tucson. Dr. Maddur has no relevant disclosures.

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TMEM16F was located predominantly at the basolateral side. TMEM16A was also located in intestinal smooth muscle cells.

Compared with wild-type mice, TMEM16 knockout mice had pronounced accumulation of lysozyme in jejunal Paneth cells suggesting a defect in Paneth cell secretion in the absence of TMEM16A and TMEM16F.

Previous studies found an accumulation of mucus in intestinal goblet cells in mice with tissue-specific knockout of TMEM16A and TMEM16F. In this study, a more detailed analysis of mucus using periodic acid-Schiff staining of duodenum, jejunum, and ileum confirmed those results and demonstrated enhanced mucus in the small intestine of knockout mice suggesting that a lack of TMEM16A or TMEM16F causes a broad secretion defect in secretory cells, including Paneth cells.

Because granules of Paneth cells contain antimicrobial peptides, cytokines, and other factors that control proliferation or epithelial cell death, researchers analyzed the presence of Gram-positive and Gram-negative bacteria in the jejunum and ileum. Compared to wild-type mice, the number of bacteria was higher in the ileum of both TMEM16A and TMEM16F knockout mice and in the jejunum of TMEM16F knockout mice, suggesting reduced antimicrobial activity in the absence of TMEM16 proteins.

"Intestinal inflammatory diseases such as Crohn's disease, necrotizing enterocolitis, and intestinal microbiota dysbiosis have been related to abnormal Paneth cell physiology," the authors wrote. "The present findings may therefore provide the basis for a novel anti-inflammatory therapy for intestinal diseases and may improve our understanding of the molecular mechanism of some of the currently available drugs."

The study was supported by the Deutsche Forschungsgemeinschaft funding program. The authors disclosed no conflicts of interest.

PNPLA3 genotype predicts cirrhosis in NAFLD

BY WILL PASS
MDedge News

Patients with nonalcoholic fatty liver disease (NAFLD) who carry two copies of the PNPLA3 p.I148M variant, may exhibit faster progression to cirrhosis, while those with this genotype who also have diabetes and indeterminate Fibrosis-4 (FIB4) scores may have the same risk of cirrhosis as patients with a high FIB4, according to investigators.

These findings suggest that NAFLD patients with indeterminate FIB4 and metabolic risk factors should routinely undergo *PNPLA3* genotyping, lead author Vincent L. Chen, MD, of the University of Michigan, Ann Arbor, and colleagues reported.

"Whether incorporating genetics into risk stratification results in meaningful improvement over clinical predictors, such as FIB4, diabetes, and obesity status, is unknown," the investigators wrote in Gastroenterology (2023 Feb 6. doi: 10.1053/j.gastro.2023.01.040). "Improved understanding of how genetics influences the rate of disease progression and how it interacts with established risk factors for advanced liver disease is crucial for genetic testing to be applicable in clinical practice."

To evaluate the risk presented by the *PNPLA3* p.I148M variant, Dr. Chen and colleagues analyzed data from two independent cohorts with 7,893 patients and 46,880 patients each.

They first characterized the relationship between *PNPLA3* genotype and cirrhosis via univariable and multivariable analyses. These efforts revealed that the genotype predicted cirrhosis in both cohorts, with associations also detected for well-documented clinical risk factors, including diabetes, obesity, and high ALT. Of note, *PNPLA3* genotype demonstrated an additive effect for cirrhosis when detected in conjunction with these risks.

Further analysis revealed that homozygous carriers of *PNPLA3* p.I148M with indeterminate FIB4 scores (1.3-2.67) and diabetes had an incidence rate of cirrhosis on par with patients who had high-risk FIB4 (greater than 2.67).

The effects of the risk allele were also made evident by comparing patients with diabetes and indeterminate FIB4 based on presence or absence of the marker. Those testing positive for two copies of *PNPLA3* p.I148M had 2.9-4.8 times greater risk of cirrhosis. Conversely, patients with FIB4 scores less than 1.3, regardless of other risk factors, had little change in cirrhosis rate regardless of *PNPLA3* status.

"We found that *PNPLA3* genotyping in conjunction with clinical risk factors may improve risk stratification in patients with NAFLD," the investigators concluded. "Although it may be possible to develop more complex polygenic risk scores for cirrhosis, these findings suggest that genotyping of *PNPLA3* alone, which is less expensive than genomewide genotyping and easier to understand, may have similar clinical applicability for NAFLD."

Dr. Chen and colleagues therefore recommended that NAFLD patients with metabolic risk factors (particularly diabetes) and indeterminate FIB4 routinely undergo *PNPLA3* genotyping, with referral to hepatology if positive for two risk alleles.

The study was supported by the American Association for the Study of Liver Diseases, National Institutes of Health, and the University of Michigan department of internal medicine. The investigators disclosed no conflicts of interest. ■

Nonalcoholic fatty liver disease is becoming globally a leading cause of cirrhosis and related complications, namely decompensation and hepatocellular carcinoma. Since NAFLD affects a large fraction of the population, and especially people with obesity, type 2 diabetes and metabolic comorbidities, it is difficult to identify those at risk of cirrhosis and liver-related versus more frequent cardiometabolic events. The first step in risk stratification is based on the calculation of simple liver fibrosis scores, such as the FIB4, but this too often leads to indeterminate results requiring additional testing.


Dr. Valenti

This study by Chen and colleagues confirmed that inherited factors play a major role in NAFLD progression to cirrhosis, with an impact comparable with the main clinical determinants. Importantly, they identified the presence of diabetes and carriage of two copies of the *PNPLA3* rs738409 variant (p.I148M), the main genetic determinant of NAFLD, as a combination that can effectively reclassify individuals with an indeterminate FIB4 test to be at high risk of cirrhosis.

These results will contribute to establish referral pathways to identify persons at high risk of liver disease, even at a young age. This may enable preventive programs based on intensified lifestyle and diabetes management, specific treatments for fibrotic NAFLD once these become available, and close surveillance for complications. What's more, therapeutic approaches directly targeting liver *PNPLA3* p.I148M are already under clinical evaluation to prevent disease progression specifically in this high-risk group.

Luca Valenti, MD, is an associate professor of internal medicine in pathophysiology and transplantation at the Università degli Studi di Milano. He is head of the Precision Lab and Biological Resource Center Unit. Dr. Valenti has no relevant disclosures.

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10.1016/j.cgh.2022.06.032), prompting the present research.

Previous studies have described a broad range of annual incidence findings for HCC in this population, from 0.6% to 5.6%, suggesting that a systematic approach was needed.

To this end, Dr. Huang and colleagues analyzed data from 18 studies that involved 148,333 patients with alcohol-associated cirrhosis. The primary analysis aimed to determine cumulative incidence rates over time, while the secondary analysis characterized the impact of participation in HCC surveillance programs.

"This meta-analysis used reconstructed individual participant data, which is considered to be the gold standard for reporting survival data because it accounts for censoring of events," the investigators noted. "The current study provides important data that are useful for clinical practice and clinical trial design."

The cumulative incidence rates of HCC were 1%, 3%, and 9% at 1 year, 5 years, and 10 years, respectively. Among 12 of the risk factors studied, smoking, diabetes, and decompensation were all significantly associated with rate of HCC.

"Therefore, patients with alcohol-associated cirrhosis should be screened for diabetes to identify the patients at high risk for HCC development," the investigators wrote. "In addition, patients with alcohol-associated cirrhosis should be advised to stop smoking, while patients with hepatic decompensation should be monitored carefully for the development of HCC if clinically appropriate."

The secondary analysis showed that HCC incidence rates were higher among patients participating in HCC surveillance programs than those who did not participate (18.6 vs. 4.8 per 1,000 person-years; $P = .001$).

"Patients with alcohol-associated cirrhosis are known to have lower HCC surveillance rates, which may be related to poor disease awareness, clinic time constraints caused by other active medical issues, and provider beliefs regarding the likelihood of adherence," the investigators noted.

Increased efforts are needed to promote surveillance in this population, they added, suggesting a range of communication pathways, including social media, traditional news outlets, and direct mailing.

Dr. Huang and colleagues also suggested that the findings should be validated in large prospective studies.

The study was funded by the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Environmental Health Sciences, the National Center for Advancing Translational Sciences, and others. Dr. Huang disclosed funding from the Singapore Ministry of Health's National Medical Research Council. ■

Pancreas cysts – What's the best approach?

Continuing pancreas cyst surveillance indefinitely is reasonable

BY LAUREN G. KHANNA, MD, MS

Pancreas cysts remain a clinical challenge. The true incidence of pancreas cysts is unknown, but from MRI and autopsy series, may be up to 50%. Patients presenting with a pancreas cyst often have significant anxiety about their risk of pancreas cancer. We as a medical community initially did too; but over the past few decades as we have gathered more data, we have become more comfortable observing many pancreas cysts. Yet our recommendations for how, how often, and for how long to evaluate pancreas cysts are still very much under debate; there are multiple guidelines with discordant recommendations. In this article, I will discuss my approach to patients with a pancreas cyst.


Dr. Khanna

At the first evaluation, I review available imaging to see if there are characteristic features to determine the type of pancreas cyst: IPMN (including main duct, branch duct, or mixed type), serous cystic neoplasm (SCA), mucinous cystic neoplasm (MCN), solid pseudopapillary neoplasm (SPN), cystic neuroendocrine tumor (NET), or pseudocyst. I also review symptoms, including abdominal pain, weight loss, history of pancreatitis, and onset of diabetes, and check hemoglobin A1c and Ca19-9. I often recommend magnetic resonance cholangiopancreatography (MRCP) if it has not already been obtained and is feasible (that is, if a patient does not have severe claustrophobia or a medical device incompatible with MRI). If a patient is not a candidate for treatment should a pancreatic malignancy be identified, because of age, comorbidities, or preference, I recommend no further evaluation.

Where cyst type remains unclear despite MRCP, and for cysts over 2 cm, I recommend endoscopic ultrasound (EUS) for fluid sampling to assist in determining cyst type and to rule out any other high-risk features. In accordance with international guidelines, if a patient has any concerning imaging features, including main pancreatic duct dilation >5 mm, solid component or mural nodule, or thickened or enhancing duct walls, regardless of cyst size, I recommend EUS to assess for and biopsy any solid component and to sample cyst fluid to examine for dysplasia. Given the lower sensitivity of CT for high-risk features, if MRCP is not feasible, for cysts 1-2 cm, I recommend EUS for better evaluation. ■

Dr. Khanna is chief, advanced endoscopy, Tisch Hospital; director, NYU Advanced Endoscopy Fellowship; assistant professor of medicine, NYU Langone Health. There are no relevant conflicts to disclose.

Pancreas cysts: More is not necessarily better!

BY SANTHI SWAROOP VEGE, MD, AGAF

Pancreas cysts are very common, incidental findings on cross-sectional imaging, performed for non–pancreas-related symptoms. The important issues in management of patients with PC in my practice are the prevalence, natural history, frequency of occurrence of high-grade dysplasia (HGD) and/or pancreatic cancer (PDAC), concerning clinical symptoms and imaging findings, indications for endoscopic ultrasound (EUS) fine-needle aspiration cytology, ideal method and frequency of surveillance, indications for surgery (up front and during follow-up), follow-up after surgery, stopping surveillance, costs, and unintentional harms of management.


Dr. Vege

Good population-based evidence regarding many of the issues described above does not exist, and all information is from selected clinic, radiology, EUS, and surgical cohorts (very important when trying to assess the publications). Cohort studies should start with all PC undergoing surveillance and assess various outcomes, rather than looking backward from EUS or surgical cohorts.

The 2015 American Gastroenterological Association guidelines on asymptomatic neoplastic pancreas cysts, which I coauthored, recommend, consistent with principles of High Value Care (minimal unintentional harms and cost-effectiveness), that two of three high-risk features (mural nodule, cyst size greater than 3 cm, and dilated pancreatic duct) be present for EUS-guided fine-needle aspiration (EUS-FNA). By the same token, they advise surgery for those with two of three high-risk features and or concerning features on EUS and cytology.

Mural nodule, cyst size greater than 3 cm, and dilated pancreatic duct must be present for EUS-guided fine-needle aspiration per 2015 AGA guidelines.

Finally, they suggest stopping surveillance at 5 years if there are no significant changes. Rigorous GRADE methodology along with systematic review of all relevant questions (rather than cohorts of 500 or fewer patients) formed the basis of the guidelines. ■

Dr. Vege is professor of medicine at the Mayo Clinic. He reported having no conflicts of interest regarding this article.

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Dear colleagues,


Dr. Ketwaroo

Pancreas cysts have become almost ubiquitous in this era of high-resolution cross-sectional imaging. They are a common GI consult with patients and providers worried about the potential risk of malignant transformation. Despite significant research over the past few decades, predicting the natural history of these cysts, especially the side-branch intraductal papillary mucinous neoplasms (IPMNs), remains difficult. There have been a variety of expert recommendations and guidelines, but heterogeneity exists in management especially regarding timing of endoscopic ultrasound, imaging surveillance, and cessation of surveillance. Some centers will present these cysts at multidisciplinary conferences, while others will follow general or local algorithms. In this issue of Perspectives, Dr. Lauren G. Khanna, assistant professor of medicine at NYU Langone Health, New York, and Dr. Santhi Vege, professor of medicine at the Mayo Clinic, Rochester, Minn., present updated and differing approaches to managing these cysts. Which side of the debate are you on? We welcome your thoughts, questions and input — share with us on Twitter @AGA_GIHN.

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.

CRC blood tests: A future without colonoscopies?

BY KERRY DOOLEY YOUNG

U.S. regulators may soon approve blood-based biomarker tests for colorectal cancer (CRC), expanding potential options for patients seeking more convenient forms of screening.

Most recently, Guardant Health announced the completion of its U.S. premarket approval application for its Shield blood test to screen for CRC. Approval by the Food and Drug Administration would position Guardant to later secure Medicare coverage for its test.

Rival companies, including Cell-Max Life, Freenome, and Exact Sciences, which already offers the stool-based Cologuard product, are pursuing similar paths in their development of blood tests for CRC.

If these companies succeed, clinicians and patients could have a choice of several FDA-approved tests in a few years.

"They're coming, and they will be increasingly widely used," said David A. Johnson, MD, professor of medicine and chief of gastroenterology at Eastern Virginia Medical School, Norfolk, who earlier in his career helped win broader insurance coverage of colonoscopy.

Blood tests for CRC have the potential to cause a shift in screening for colon cancer.

Screening colonoscopies ultimately could be largely phased out in the years ahead in favor of highly sensitive noninvasive tests, if the blood tests do as well as expected, said John M. Carethers, MD, AGAF, president of the American Gastroenterological Association.

'Holy grail?'

"A blood test for cancer screening has been the 'holy grail' ever since the carcinoembryonic antigen blood test in the 1960s was claimed to have nearly 100% sensitivity and specificity – but turned out not to – for colorectal cancer," wrote David F. Ransohoff, MD, a gastroenterologist at the University of North Carolina at Chapel Hill, in a 2021 article (J Natl Cancer Inst. 2021 Feb 1;113[2]:109-1). Dr. Ransohoff has studied noninvasive CRC screening for decades.

"MCD technology offers the potential to detect asymptomatic cancer at several organ sites with a simple blood test, often called a liquid biopsy."

There is a great allure in the idea of such multi-cancer detection (MCD) tests. "MCD technology offers the potential to detect asymptomatic cancer at several organ sites with a simple blood test, often called a liquid biopsy," according to a National Cancer Institute FY24 budget request report.

Several companies are selling MCD tests, some of which include CRC components. Among the best-known MCD tests now sold is Grail's Galleri. At this time, however, the Galleri test, which tests for 50 types of cancer, should be used in addition to recommended colon cancer screening tests, such as colonoscopy, the company's website says.

Guardant says its CRC-specific blood test should only complement screening tools, including colonoscopy, not replace them.

The prospect of phasing out the most commonly used CRC screening test – colonoscopy – may be appealing, but it would require a big shift for a field in which procedures have dominated. According to a report from the Centers for Disease Control and Prevention (Morb Mortal Wkly Rep. 2020;69:314), in 2018, 67% of U.S. adults aged 50-75 years met the U.S. Preventive Services Task Force recommendations for CRC screening, and overall, 60.6% had a colonoscopy in the past 10 years.

Still, the National Cancer Institute and the FDA have signaled the potential they see in MCD tests. The NCI highlighted its plans to aid MCD test development as part of its budget request for fiscal year 2024. The NCI is preparing to launch a 4-year pilot study for MCD tests to enroll 24,000 people aged 45-70 years. The study is intended as groundwork for a randomized controlled trial that will enroll 225,000 people.

The FDA has shown an interest in helping companies bring blood tests for cancer detection to market through its breakthrough device designation – a sign that the FDA places great priority on a product and seeks to streamline the application and review process.

CellMax Life appears to be the only CRC-specific screening blood test to have received a breakthrough device designation from the FDA, Atul Sharan, MS, MBA, cofounder and chief executive officer of CellMax Life, said in an email.

Lance Baldo, MD, Freenome's chief medical officer, said in an interview that the FDA may be reviewing parts of their application in 2024, allowing for a potential 2025 launch of a blood test for asymptomatic people at average risk for CRC.

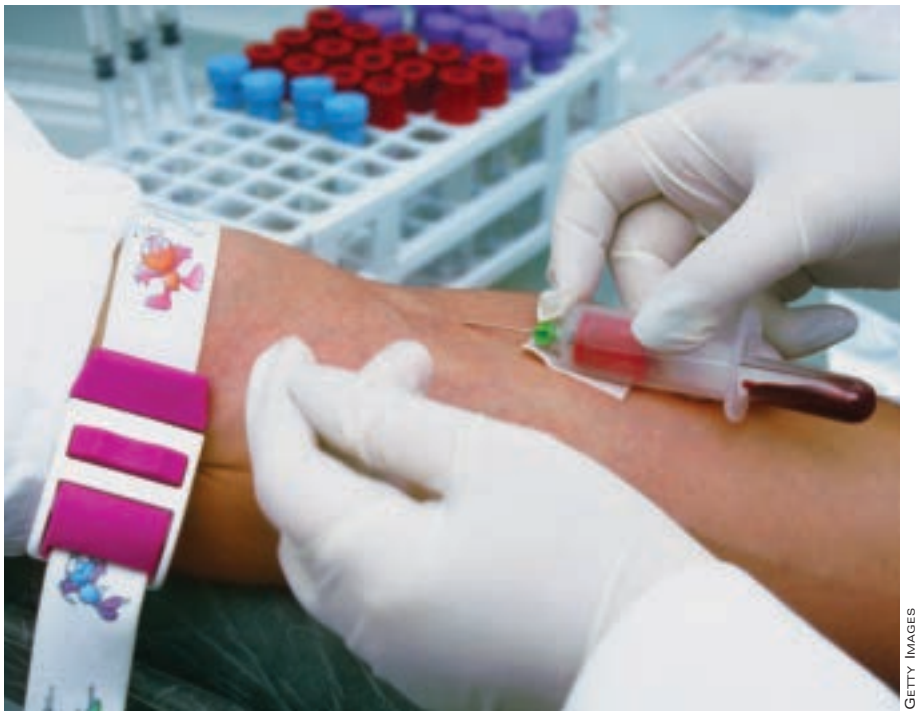
A spotty track record

Before anyone gets too excited about the prospect of phasing out screening colonoscopy, it's important to remember that CRC blood tests have proven disappointing in the past.

Germany's Epigenomics, for example, secured the first FDA approval for a CRC blood test, Epi ProColon, in 2016. But the company did not receive Medicare coverage for the test. In a 2021 memo explaining the decision, the Centers for Medicare & Medicaid Services noted that, given more reliable alternatives, including stool-based tests, the Epi ProColon would result in harm to some patients.

CMS also does not cover Grail's blood test, which has a list price of $949, though the company has secured reimbursement arrangements with several self-insured employers and insurers, such as Point32Health.

But CMS officials have acknowledged the strong interest in CRC blood tests.



GETTY IMAGES

Regulators may soon approve colorectal cancer blood-based biomarker tests.

In that 2021 memo, the agency also outlined its requirements for Medicare coverage. CMS said it will cover blood-based screening tests for certain patients if these products meet the following standards:

- Receive FDA market authorization with an indication for CRC screening.
- Have proven test performance characteristics for a blood-based screening test with sensitivity of at least 74% and specificity of at least 90% in the detection of CRC, compared with the recognized standard (which at this time is colonoscopy) as minimal threshold levels, based on the pivotal studies included in the FDA labeling.

In February 2023, CellLife Max presented data at ASCO Gastrointestinal Cancers Symposium that its blood test had sensitivity of 92.1% for detection of CRC and 54.5% for detection of advanced adenomas, at 91% specificity.

Prior to that, in December 2022, Guardant issued a press release with study results that met the CMS standard. The test had sensitivity of 83% in detecting individuals with CRC. Specificity was 90%, the company said. That translates to a false-positive rate of just 10%.

While such results look promising, Asad Umar, DVM, PhD, the chief of gastrointestinal and other cancers at NCI's division of cancer prevention, said physicians should be cautious when giving advice or answering questions about MCD tests, given limited data from prospective studies about their effect on health outcomes.

Even among physicians already using some MCD tests to screen patients, there is a lot of concern about false positive results that require diagnostic workup and false-negative results that lead to a false sense of assurance, Dr. Umar said.

"Screening is a process and not just a test. The process involves follow-up testing for any positive test findings," Dr. Umar said. "At this point, doctors should inform patients that there is not sufficient data to know how best to use these tests."

Hurdles to broad acceptance

For companies seeking broad acceptance of a CRC blood test, two of the three major steps needed are securing FDA approval and Medicare coverage. The last step would be getting an A or B recommendation from the USPSTF, which would mandate coverage by health plans.

This is the "big trifecta," Dr. Baldo said.

In the USPSTF's current colon cancer screening recommendations, issued in 2021, it gave an A grade for CRC screening for adults aged 50-75 years and a B grade for those aged 45-49 years. The USPSTF's recommended forms of screening include colonoscopy, high-sensitivity guaiac fecal occult blood (gFOBT), fecal immunochemical test (FIT), flexible sigmoidoscopy (FS), stool DNA, and/or computed tomographic colonography.

The USPSTF says more research is needed to establish the accuracy and effectiveness of emerging screening technologies, such as blood or serum tests.

If CRC blood tests eventually win FDA approval, the USPSTF would likely provide guidance to clinicians on how patients can use them as a screening option.

Dr. Ransohoff noted that the mission of the USPSTF is different from that of the FDA and CMS. The FDA's approach on medical tests is to consider overall safety and efficacy, as does CMS, but neither agency makes recommendations, nor does it perform its own rigorous quantitative assessment of benefit versus harm. The USPSTF, however, does its own detailed evidence-based reviews of the benefit versus harm of products, Dr. Ransohoff said.

"To me, the Task Force is the gold standard," Dr. Ransohoff said. "You have to jump through the hoops with the FDA and CMS for making claims, to enable use, and to help get payment. But the Task Force looks at the choices and the consequences in a quantitative way and makes specific practice recommendations."

What the future may hold

Dr. Carethers sees a future in which highly sensitive blood tests are able to largely replace screening colonoscopies. He said that colonoscopies would be used for people who are most in need of diagnosis and treatment. Dr. Carethers addressed these points during an AGA podcast released in January (https://rb.gy/4y0cl).

In 20-25 years, colonoscopies may be only a therapeutic procedure, much like endoscopic retrograde cholangiopancreatography is now, Dr. Carethers added.

Even if CRC-specific blood tests prove to be effective screening tools, Dr. Ransohoff stressed that colonoscopy will survive. Many people will eventually need to undergo colonoscopy as a diagnostic procedure following a positive blood-based test result, and some may also opt for screening colonoscopies in lieu of frequent blood tests.

And, overall, physicians and patients will need to weigh the tradeoffs of a noninvasive test that can diagnose only CRC versus a screening colonoscopy that offers preventative treatment as well.

"The best intent for screening is prevention of cancer, not detection of cancer," Dr. Johnson said. ■

Semaglutide falls short for NASH-related cirrhosis

BY CAROLYN CRIST

Semaglutide didn't significantly improve liver fibrosis or achieve resolution of nonalcoholic steatohepatitis–related compensated cirrhosis, compared with placebo, according to a phase 2 trial. "There are limited data on whether any therapy is effective in patients with NASH cirrhosis," lead author Rohit Loomba, MD, founding director of the NAFLD Research Center at the University of California, San Diego, said in an interview. "Although semaglutide did not succeed in improving histological fibrosis, it had success in improving other clinically important parameters, such as cardiometabolic risk factors, liver enzymes, liver fat, and noninvasive biomarkers of fibrosis," he said.

The study was published online in The Lancet Gastroenterology & Hepatology (2023 Mar 16. doi: 10.1016/S2468-1253[23]00068-7).

Dr. Loomba and colleagues conducted a double-blind, placebo-controlled phase 2 trial that enrolled 71 patients at 38 centers in the United States and Europe between June 2019 and April 2021. Adults with biopsy-confirmed NASH-related cirrhosis and a body mass index (BMI) of at least 27 kg/m^2 were randomly assigned 2:1 to receive once-weekly subcutaneous semaglutide at 2.4 mg or a visually matching placebo.

Patients, investigators, and outcomes analysts were masked to the treatment assignment. The primary endpoint was the proportion of patients with an improvement in liver fibrosis of one stage or more without a worsening of NASH after 48 weeks, which was measured through biopsy. Among the 71 patients, 47 were randomly assigned to the semaglutide group and 24 to the placebo group. About 90% completed treatment, and 63 had evaluable paired biopsies for primary endpoint assessment.

Between the groups, 49 participants (69%) were women and 22 were men. The average age was 59.5 years, and the average BMI was 34.9. About 75% of patients had diabetes at baseline, with an average hemoglobin A1c of 7.1%.

After 48 weeks, researchers found no statistically significant difference between the groups in the proportion of patients with an improvement in liver fibrosis of one stage or more without worsening of NASH. In the semaglutide group, five patients (11%) had an improvement, compared with seven patients (29%) in the placebo group (odds ratio, 0.28; 95% confidence interval, 0.06-1.24, *P* = .087).

There also wasn't a significant difference between groups in the proportion of patients who achieved NASH resolution. In the semaglutide group, 16 patients (34%) had resolution, compared with 5 patients (21%) in the placebo group (OR, 1.97; 95% CI, 0.56-7.91; *P* = .29).

It's important to note that NASH can't be oversimplified as a "matter of weight." Significant weight loss didn't result in histologic improvement, which means other strategies are needed.

A lower proportion of patients had an improvement in liver fibrosis stage with semaglutide versus placebo. However, the semaglutide group had significantly greater improvements in liver steatosis (but not stiffness), liver fat volume, procollagen 3 peptide, and liver enzymes such as ALT, AST, and gamma-glutamyltransferase.

Body weight decreased by 8.83% in the semaglutide group, compared with 0.09% in the placebo group, which was a significant difference. BMI, waist circumference, triglycerides, and VLDL cholesterol were also significantly lower in the semaglutide group, but total cholesterol and blood pressure measurements weren't significantly different. Among those with type 2 diabetes, A1c also decreased in the semaglutide group but did not in the placebo group.

Similar proportions of patients in each group reported adverse events. The most common adverse events in the semaglutide and placebo groups were nausea (45% and 17%), diarrhea (19% and 8%), and vomiting (17% and none), which mainly occurred during treatment initiation or dose escalation. No patients withdrew from the trial because of adverse events, although five had a dose reduction. Hepatic and renal function remained stable after semaglutide treatment, and there were no decompensating events or deaths.

"GLP-1 analogue exposure – among patients with compensated cirrhosis who suffer from morbid

Continued on following page

Be aware of hepatic encephalopathy, dementia overlap

BY CAROLYN CRIST

Dementia frequently coexists with hepatic encephalopathy (HE) in patients with cirrhosis but doesn't correlate with other decompensating events, according to a new study of U.S. veterans.

The overlap between dementia and HE was also independent of alcohol use, brain injury, age, and other metabolic risk factors.

"The aging of patients with cirrhosis leads us to encounter several individuals who may be prone to both of these diseases," said senior author Jasmohan Bajaj, MD, AGAF, a professor of gastroenterology, hepatology, and nutrition at Virginia Commonwealth University Medical Center and GI section of the Central Virginia Veterans Healthcare System in Richmond.

"Given the epidemic of metabolic syndrome and alcohol, consider excluding cirrhosis in your patient [for] whom the presumptive diagnosis is dementia, since they could have concomitant HE," he said. "On the flip side, in those with HE who have predominant long-term memory issues and persistent cognitive changes, consider consulting a neuropsychiatrist or neurologist to ensure there is a resolution of the underlying disease process."

The study was published online in The American Journal of Gastroenterology (2023 Feb 3. doi: 10.14309/ajg.0000000000002189).

Using data from the VA Corporate Data Warehouse, researchers identified veterans with cirrhosis who received VA care between October 2019 and September 2021 and compared baseline characteristics between the cohorts based on the presence or absence of dementia.

The analysis included 71,522 veterans with cirrhosis (96.2% men, mean age 66 years). The most common etiologies of cirrhosis were alcohol and hepatitis C, followed by nonalcoholic steatohepatitis (NASH). The group also included veterans with predominantly compensated cirrhosis and a median MELD-Na score of 9. The MELD-Na score gauges the severity of chronic liver disease using values such as serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time and sodium to predict survival. Among those with cirrhosis, 5,647 (7.9%) also had dementia diagnosis codes. This rate is higher than the prevalence of dementia in the general population and equivalent to the rate of dementia in veterans without cirrhosis who are older than 65.

Veterans with dementia tended to have higher MELD-Na scores. They were more frequently diagnosed with alcohol-related cirrhosis, alcohol and tobacco use disorder, diabetes, chronic kidney disease, chronic heart failure, brain trauma, and cerebrovascular disease.

The presence of decompensating events was significantly associated with dementia. In subsequent analyses of individual decompensating events, the strongest association was with HE, while ascites or variceal bleeding did not add to the risk. When HE was defined as patients who filled prescriptions for lactulose or rifaximin, the frequency of patients with HE decreased from 13.7% to 10.9%. In an analysis with HE as the decompensating event, the association between HE and dementia remained significant compared to when HE was defined by diagnostic codes alone.

"We were surprised by the high proportion of patients with dementia who also had cirrhosis, and given the genuine difficulty that clinicians have with defining HE vs. dementia, we were not very surprised at that overlap," Dr. Bajaj said. "We were also surprised at the specificity of this overlap only with HE and not with other decompensating events, which was also independent of head injury, alcohol use, and PTSD."

The study received no financial support. The authors reported no potential competing interests. ■

Continued from previous page

obesity and type 2 diabetes – for the treatment of diabetes appears to be well-tolerated and may be safe," Dr. Loomba said. "Further studies are needed in this study population."

Dr. Loomba and colleagues are continuing research around risk factors linked to advanced fibrosis, such as type 2 diabetes, a family history of cirrhosis, and the presence of key genetic risk alleles. Gut dysbiosis also appears to increase the risk for advanced fatty liver disease, he said.

"As these patients are oftentimes excluded from initial randomized controlled trials, we have significantly less information on how to address obesity, type 2 diabetes, and NASH in these patients," Fernando Bril, MD, a physician-scientist focused on NASH-related research at the University of Alabama at Birmingham, said in an interview.

Dr. Bril, who wasn't involved with this study, wrote an accompanying editorial in The Lancet Gastroenterology & Hepatology (2023 Mar 16. doi: 10.1016/S2468-1253[23]00069-9).

Patients with NASH-related cirrhosis may have progressed to a point of the disease where fibrosis regression may be more difficult to achieve, he said. "This emphasizes that early diagnosis of patients with NASH is crucial," he said.

"Therefore, primary care providers, endocrinologists, and diabetologists need to have a low threshold to suspect liver disease in patients with overweight, obesity, and/or type 2 diabetes. Only this will allow for early initiation of therapy, which may delay the progression of liver disease."

In further research, investigators may want to consider the lack of NASH resolution, a result that could be caused by this study being underpowered, Dr. Bril noted. The trend in resolution in this study appeared similar to improvements seen in NASH patients without cirrhosis in other studies, he said. The weight reduction and improved diabetes control in this group also shows promise.

"While a purist may be adamant that this was a negative study for histological outcomes, it is essential to take note of the positive results in many secondary outcomes," he said. "Improving cardiometabolic risk in these patients is essential because many still die of cardiovascular disease and not liver-related complications."

It's important to note that NASH can't be oversimplified as "a matter of weight," Dr. Bril said. Significant weight loss in the study didn't result in histologic improvement, which means other strategies are needed. "Negative results from this study emphasize that monotherapy may not be enough to improve NASH and liver fibrosis," he said. "In a similar way we treat type 2 diabetes and hypertension with combination therapy, we need to consider a similar approach for patients with NASH."

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