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2007-10-Year Anniversary-2017

VOL. 11 NO. 5 MAY 2017

GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

COURTESY RUTGERS UNIVERSITY

Dr. Brian Strom, of Rutgers University, led the group that produced the report, which maintains that we have the tools to end hepatitis now.

Report offers road map for eliminating hepatitis in U.S.

BY JENNIE SMITH
Frontline Medical News

An ambitious new report by the National Academies of Sciences, Engineering, and Medicine lays out a detailed path by which some 90,000 deaths from hepatitis B and C infection could be prevented by 2030.

The National Academies, a group of nongovernmental advisory bodies that includes the former Institute of Medicine, said that "the tools to prevent these deaths" exist – namely vaccination to prevent new hepatitis B infections and antiviral drugs, including new oral medications that can cure chronic hepatitis C infections within months.

The authors of the 200-plus-page report, led by Brian Strom, MD, MPH, of Rutgers University in Newark, N.J., calculate that deaths from hepatitis B infection could be halved by 2030 if 90% of patients are diagnosed, if 90% of those diagnosed are connected to care, and if 80% of those for whom treatment is indicated receive it. Treating everyone with chronic hepatitis C would reduce new infections by 90% by 2030, while reducing related deaths by 65%, Dr. Strom

See **Road map** · *page 20*

Liver disease to grow as indication for bariatric surgery, expert predicts

BY TED BOSWORTH
Frontline Medical News

PHILADELPHIA – There is a long list of benefits from bariatric surgery in morbidly obese patients, but prevention of end-stage liver disease and the need for a first or second liver transplant is likely to grow as an indication, one expert said at Digestive Diseases: New Advances, held by Rutgers, the State University of New Jersey, and Global Academy for Medical Education.

"Bariatric surgery is associated with significant improvement not just in diabetes, dyslipidemia, hypertension, and other complications of metabolic disorders but for me more interestingly, it is effective for treating fatty liver disease where you can see a 90% improvement in steatosis," reported Subhashini Ayloo, MD, chief of minimally invasive robotic hepato-pancreato-biliary surgery and liver transplantation at New Jersey Medical School, Newark, at the meeting.

Trained in both bariatric surgery and liver transplant, Dr. Ayloo predicts that these fields will become increasingly connected because of the obesity epidemic and the related rise in nonalcoholic fatty liver disease (NAFLD). Dr. Ayloo reported that bariat-

See **Bariatric** · *page 25*

INSIDE

A viral inducer of celiac disease?

BY JIM KLING
Frontline Medical News

A viral infection may be the culprit behind celiac disease, which is caused by an autoimmune response to dietary gluten. The findings are based on an chers believe that a reovirus may disrupt intestinal immune homeostasis in susceptible individuals as a result of infection during childhood.

According to in vitro and mouse studies carried out by the researchers, one strain of reovirus suppresses peripheral regulatory T-cell conversion and promotes T helper 1 immune response at sites that normally induce tolerance to dietary antigens. The work appeared in the April issue of Science (2017;356:44-50).

See **Celiac** · *page 26*

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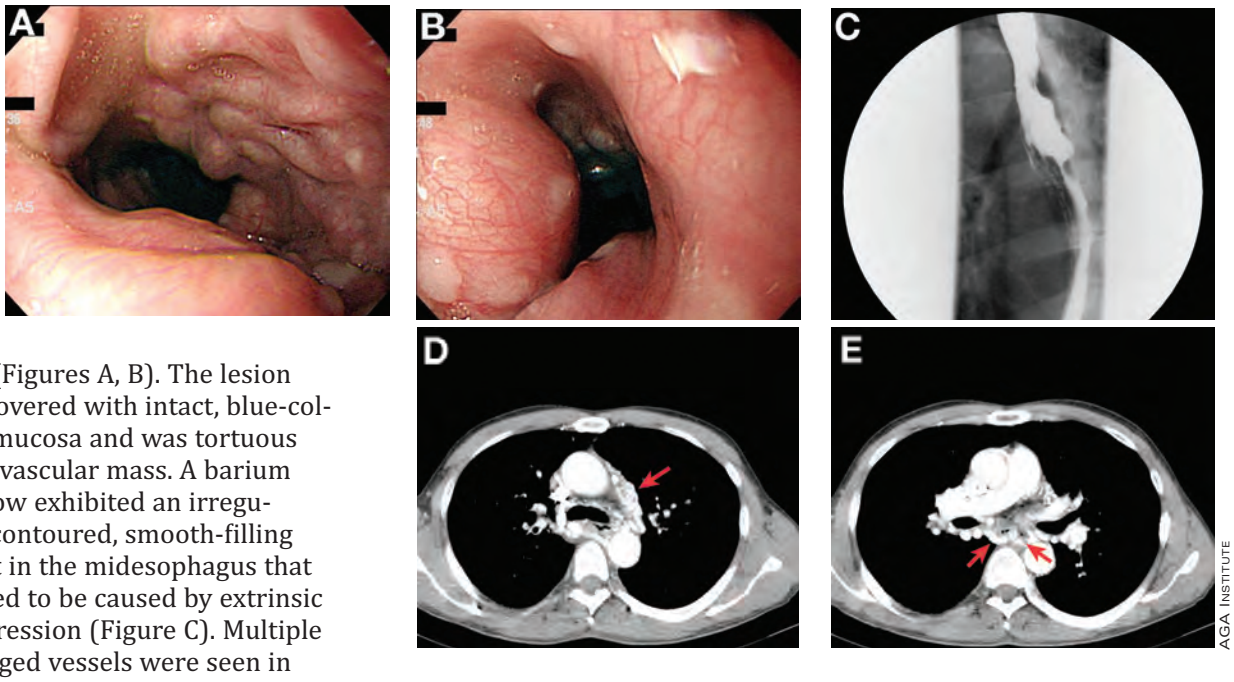
CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

By Ki-Hyun Ryu, MD, Tae-Hee Lee, MD, and Taek-Geun Kwon, MD. Published previously in Gastroenterology (2013;144;35, 253).



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A 46-year-old man was referred with unusual esophageal varices. He presented with a foreign-body sensation when swallowing food, accompanied by mild chest discomfort for 1 month. His medical history and family history were unremarkable. Vital signs were stable, and there was no evidence of liver cirrhosis on physical examination. Endoscopic examination revealed an irregular-shaped, elevated lesion in the midesophagus (Figures A, B). The lesion was covered with intact, blue-colored mucosa and was tortuous like a vascular mass. A barium swallow exhibited an irregularly contoured, smooth-filling defect in the midesophagus that seemed to be caused by extrinsic compression (Figure C). Multiple engorged vessels were seen in the pericardial area, prevascular space, and paraesophageal area on contrast-enhanced computed tomography (Figures D, E). Markedly dilated enhancing vessels, probably veins, were noted on the right side of the esophagus at the level of the lower trachea.

The diagnosis appears on page 36.

LETTER FROM THE EDITOR: Spring brings flowers and liver stories

Happy spring (finally, for many of us)! This month's issue of *GI & Hepatology News* is "weighted" toward liver. The decrease in hepatitis C–related liver disease means that steatohepatitis will emerge as the most frequent cause of cirrhosis and transplantation. Finding medical therapies to slow obesity-related liver damage has proven challenging. Bariatric surgery may be the best option for patients, as discussed by one of our lead stories. Another page-1 story lays out a road map to eliminate viral hepatitis in the United States, a situation unheard of until direct-acting antiviral agents were developed.

A couple stories about celiac disease will be of interest, including one that discusses a viral etiology (albeit, this concept is based on an animal study). A second story focuses on the prevalence of sprue in children.

DR. ALLEN

AGA is working hard for you, which is demonstrated in this issue. First, there is the continuing controversy regarding maintenance of certification (MOC). *Continued on following page*

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GI & HEPATOLOGY NEWS is the official newspaper of the American Gastroenterological Association (AGA) Institute and provides the gastroenterologist with timely and relevant news and commentary about clinical developments and about the impact of health care policy. Content for **GI & HEPATOLOGY NEWS** is developed through a partnership of the newspaper's medical board of editors (Editor in Chief and Associate Editors), Frontline Medical Communications Inc. and the AGA Institute Staff. "News from the AGA" is provided exclusively by the AGA, AGA Institute, and AGA Research Foundation. All content is reviewed by the medical board of editors for accuracy, timeliness, and pertinence. To add clarity and context to important developments in the field, select content is reviewed by and commented on by external experts selected by the board of editors.

POSTMASTER Send changes of address (with old mailing label) to GI & Hepatology News, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.

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GI & HEPATOLOGY NEWS (ISSN 1934-3450) is published monthly for $230.00 per year by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Phone 973-206-3434, fax 973-206-9378

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FLASHBACK TO 2011

Barrett's esophagus, named after Australian-born thoracic surgeon Norman Barrett in the 1950s, is now recognized as an important risk factor for esophageal adenocarcinoma. Estimating the magnitude of this risk has proved challenging, however, as early studies of Barrett's esophagus tended to overestimate cancer risk because of small sample sizes and selection bias. Accurate risk estimation has profound implications for whether and how to identify and monitor patients with Barrett's esophagus as part of a cancer-prevention strategy.

The December 2011 issue of *GI & Hepatology News* highlighted an influential study by Frederik Hvid-Jensen, MD, and his colleagues from Aarhus (Denmark) University that harnessed the power of Danish population-based registries to estimate the incidence of esophageal adenocarcinoma and high-grade dysplasia among patients with Barrett's esophagus. Published in the New England Journal of Medicine (2011;365:1375-83), the study utilized data from Denmark's national pathology and cancer registries to calculate the incidence of adenocarcinoma among patients with Barrett's esophagus, compared with the general population. The study was unique in that there was nearly no loss to follow-up and no referral bias because of the nature of the registry.

The incidence of esophageal adenocarcinoma among patients with Barrett's esophagus was found to be only 1.2 cases/1,000 person-years, roughly four to five times lower than some rates previously reported. This conclusion added fuel to an already growing skepticism regarding the utility of aggressive endoscopic surveillance programs and encouraged less intensive surveillance recommendations than espoused by some gastroenterology guidelines at the time. It is worth noting that even our current attenuated strategy of surveillance every 3-5 year remains controversial, given conflicting evidence regarding whether endoscopic surveillance improves overall outcomes to justify the increased costs for surveillance. As elegantly stated by the accompanying editorial, "the problems with the screening and surveillance strategy for patients with Barrett's esophagus lie not in the logic but in the numbers."


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Few Heart Patients Need Antibiotics Before Procedures
AHA guidelines will change GI practice.
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Capsule Endoscopy Finds Colon Polyps
Percentage of Patients Who Progressed To Esophageal Adenocarcinoma
INSIDE
Surgical Volume
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Megan A. Adams, MD, JD, MSc, is a general gastroenterologist at Veterans Affairs, an investigator in the VA Center for Clinical Management Research, and a lecturer in gastroenterology at the University of Michigan, all in Ann Arbor. She currently serves as chair-elect of the AGA Quality Measures Committee and is an associate editor of GI & Hepatology News.

Continued from previous page

The AGA has strongly advocated to eliminate the 10-year high-impact closed-book examination (now an anachronism). ABIM is now offering the option of an open-book 2-year exam, and is working on other proposals for MOC, which you will need to become familiar with in order to contribute a voice of reason to the process.

Additionally, this month we highlight the AGA Obesity Practice Guide, DDSEP® 8, and a new clinical guideline concerning transient elastography.

We close this month's issue with a discussion from Raymond Cross, MD, and Sunanda Kane, MD, AGAF, about telemedicine and its impact on gastroenterology. There are multiple examples of how telemedicine is changing our practices and providing hope for increased efficiencies and leveraged resources.

I hope you enjoy this issue and I hope to see you all at Digestive Disease Week.®

John I. Allen, MD, MBA, AGAF
Editor in Chief

ABIM turns MOC page with open-book 2-year test

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – The way the president of the American Board of Internal Medicine, Richard J. Baron, MD, sees it, maintenance of certification (MOC) is more important than ever, because trust in the medical profession "is under assault right now in all kinds of ways."

So, to help "bring clarity to uncertainty," ABIM is continuing its makeover of the MOC process. Beginning in 2018, an open-book option to test every 2 years will be available for physicians who are certified in internal medicine and for those in the subspecialty of nephrology. These options become available to gastroenterologists in 2019.

Both the 10-year long-form assessment and the shorter 2-year assessment options will be open book, "meaning physicians will have access to an online reference while they're taking the exam," said Yul D. Ejnes, MD, who is a member of ABIM's board of directors and serves on the ABIM's internal medicine specialty board.

Known as the "Knowledge Check-In," the 2-year assessment is a shorter, "lower stakes" option that can be taken at home, in an office, or at a testing facility. The check-ins will be scheduled 4-6 times per year, with 10-year exams remaining available twice per year. The open-book 2-year assessments will be about 3 hours in length.


DR. BARON

"It's a more continuous way of learning and assessing, because the way we'll do feedback is going to change," explained Dr. Ejnes, who practices in Cranston, R.I. "You'll know right away whether you were successful or not with the assessment, as opposed to having to wait a couple of months, which happens with the 10-year assessment. Then you'll get more feedback later helping to identify areas where you may be a little weaker and need to work out things."

"It remains to be seen whether this new system is an improvement for GI learners. AGA's educators will compare the changes offered by ABIM against our principles for MOC reform," said Timothy C. Wang, MD, AGAF, President of AGA. "Reforming the MOC process is a high and long-standing priority for AGA. We have pushed ABIM to offer a system that reflects the realities of practice and how adults learn – and we'll continue to fight for these principles."

In general, physicians will need to either take the 2-year assessments or pass the 10-year assessment within 10 years of their last pass of the 10-year exam. Those who fail two successive 2-year assessments will have to take the 10-year exam. However, unsuccessful performance on the 2-year assessment in 2018 will not have a negative impact on certification or MOC participation status.

"It won't count as one of the two opportunities you have before you have to go to the 10-year exam," Dr. Ejnes said. Why a 2-year period instead of a 5-year option, for example? A shorter time frame will allow the

Continued on following page

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ABIM to move to a more modular approach to test material, Dr. Ejnes explained. For now, the 2-year assessments will be breadth-of-discipline exams.

Physicians whose certification expires in 2017 will need to take the 10-year exam – as Dr. Ejnes noted he himself was forced to do. "You cannot wait until 2018," he cautioned. "That's important, because if you let your certification lapse, you can't enter the certification pathway. The prerequisite is that you need to be in good standing with your certification."

The open-book Knowledge Check-Ins and 10-year assessments are slated to expand to eight subspecialties in 2019 and nine more in 2020.

Linking MOC and trust

Speaking at the annual meeting of the American College of Physicians, Dr. Baron said that false and misleading information circulated widely on Facebook and other social media channels runs the gamut of health issues, from falsified studies about purported links between vaccines and autism to stories of miracle cures for any number of ailments.

"It's not just vaccines people are questioning," said Dr. Baron, ABIM's president and CEO. "There are erosions of trust in government, and there's the tenacity and power of wildly inaccurate information. You will be dealing with patients who tenaciously believe things that you know not to be true. You will need to find ways to build trust, credibility, and relationships based on their trusting that what you're saying is really in their interest."

U.S. physicians aren't secure in the shaky trust landscape. In fact, globally, the United States ranks 24th in public trust level of physicians by country (N. Eng. J. Med. 2014 Oct 23;371[17]:1570-2).

"The confidence in the medical system today is lower than the confidence in police or in small business," Dr. Baron said. "That's [the view] people are bringing into your offices every day. I don't think we can assume that deference and trust are given to doctors, that the privileged role that society affords us is something that we're going to have forever. We all have to think how trust is built in the new world."

'It remains to be seen whether this new system is an improvement for GI learners. AGA's educators will compare the changes offered ... against our principles for MOC reform.'

Will patients value MOC?

During a question and answer session at the ACP session, Anne Cummings, MD, an internist who practices in Greenbrae, Calif., asked the ABIM for support in educating the general public about what it means to be treated by a board-certified physician.

"I had a naturopath tell me the other day that she had the same training as I had," Dr. Cummings said. "I was floored, but I think that patients don't know the difference."

Dr. Baron agreed ABIM needs to do more to promote the value of certification among patients. But he also called on board-certified physicians to deliver the value message directly to their own patients.

Other attendees recommended that ABIM expand the number of ways physicians can earn MOC points, and they expressed concern about the time MOC takes away from their daily practice.

For regular updates on the MOC process, physicians can subscribe to the ABIM's blog at transforming.abim.org.

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MedPAC: Medicare Part B drug payment cuts, shared savings could save $5 billion

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – Reducing the amount physicians are paid for drugs administered in their offices and introducing shared savings could save Medicare up to $5 billion over 5 years, according to recommendations from the Medicare Payment Advisory Commission.

Those MedPAC recommendations to Congress include cutting physicians' average sales price add-on percentage, as well as an alternative purchasing initiative called the Drug Value Program that would allow shared savings through more effective pharmaceutical utilization.

"It is our obligation to deal with the escalation of the cost of drugs, including in this case those that are paid through Medicare Part B," MedPAC Chairman Francis J. Crosson, MD, said during a MedPAC meeting April 6. "We have come up with a recommendation, and it consists necessarily of a set of parts that we believe are balanced in a number of ways."

Physicians should not be in a position to provide Part B drugs at a financial loss, Dr. Crosson noted. But the current 6% add-on to average sales price (ASP) "overpays many physicians and institutions, and is inherently a cost-ineffecient payment system for the Medicare program," he added.

Dr. Crosson also noted that current free-market principles do not seem to be working effectively to keep drug costs down.

MedPAC's proposal is designed to strengthen market dynamics for Part B drugs by "creating more equilibrium between the buyer and the seller than currently exists," Dr. Crosson explained. An alternative reimbursement system will lower overall drug costs for patients while preserving quality and sharing savings with physicians, he said.

If implemented, the proposals could save Medicare between $250 million and $750 million in the first year, and between $1 billion and $5 billion within 5 years. MedPAC staff said.

All present MedPAC members (with one member not present) voted unanimously in favor of moving the two-part recommendation forward to Congress.

The first part, which would start in 2018, would alter the current Part B drug payment process. Currently, doctors receive ASP plus 6%, or wholesale acquisition cost (WAC) plus 6% for drugs without sufficient ASP history.

The proposal would enhance ASP reporting, including requiring more manufacturers to submit data and increasing fines by an unspecified amount for those that fail to meet reporting standards. The WAC add-on percentage would be reduced to 3%.

An inflation index would be applied to ASP and would trigger automatic rebates if ASP climbs faster than inflation. Finally, billing codes for biosimilars and their reference products would be combined.

Under the second part of MedPAC's recommendation, in 2022 providers would face a choice: Continue to have Part B drugs paid for under the ASP scheme with a reduced add-on percentage of 3%, or take part in the Drug Value Program.

Under the Drug Value Program, physicians would sign up with one of several vendors that would be charged with negotiating prices for Part B drugs. Physicians would pay the negotiated prices for the drugs. Vendors would have standard formulary tools, such as prior authorization, tiering, and step-therapy. For a very small subset of drugs with no competition in the marketplace, the proposal includes a binding arbitration process, the specific details to be determined later.

Savings generated from participating in the Drug Value Program would be shared with providers, much like other value programs that provide opportunities for shared savings in exchange for assuming a level of risk.

It was the binding-arbitration process that garnered the most concern from commission members.

"I am absolutely opposed to arbitration," Amy Bricker, vice president of supply chain strategy at Express Scripts, St. Louis, said. "The message that the commission is sending is that we believe in free markets, but then we don't. The free market today would allow for many of the things that we are attempting to do with the DVP."

She called for more detailed discussion on the arbitration process. Her concerns were echoed by other commission members. "I don't think that arbitration ultimately results in lowering the pricing," Ms. Bricker added, suggesting it could also open the door to collusion between DVP vendors.

The proposal will be included in MedPAC's June 2017 report to Congress.

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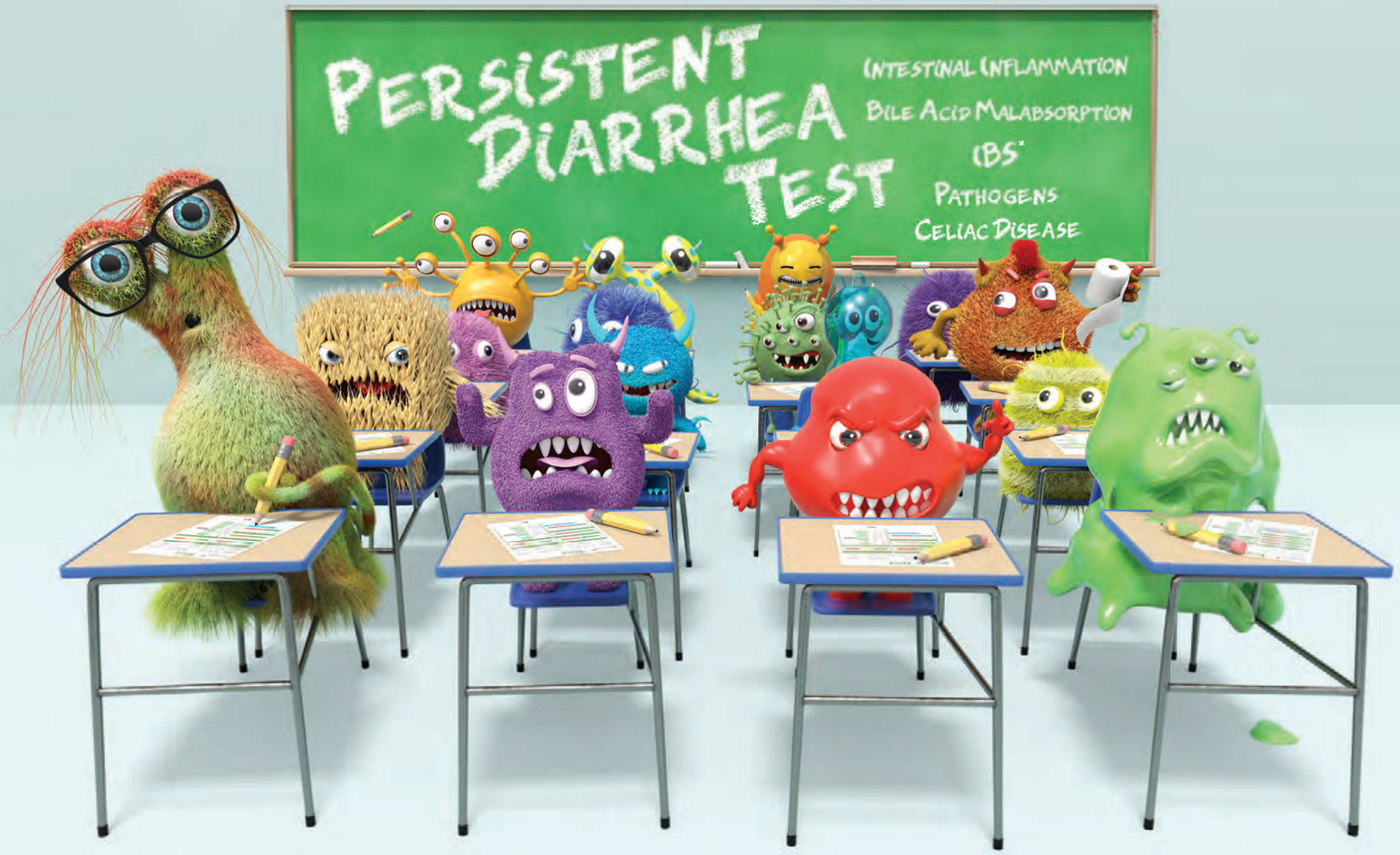

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Elbasvir, grazoprevir beat HCV in compensated cirrhosis

BY AMY KARON
Frontline Medical News

Twelve weeks of combination therapy with elbasvir and grazoprevir (EBR/GZR) achieved sustained virologic response in 98% of treatment-naive patients with compensated cirrhosis and chronic hepatitis C virus (HCV) genotype 1, 4, or 6 infections, and in 89% of treatment-experienced patients, according to a pooled analysis of six industry-sponsored trials.

Concomitant ribavirin offered "no incremental benefit" for treatment-naive patients, while 16 or 18 weeks of EBR and GZR with ribavirin achieved SVR12 in 100% of treatment-experienced patients, wrote Ira M. Jacobson, MD, of Mount Sinai Beth Israel and Icahn School of Medicine at Mount Sinai, New York, and his associates. The report was published in the May issue of Gastroenterology (doi: 10.1053/j.gastro.2017.01.050).

Regardless of treatment history, genotype 1a patients with resistance-associated variants (RAV) in HCV nonstructural protein 5A (NS5A) needed ribavirin to achieve sustained virologic response (SVR) rates above 90%, the researchers emphasized. "Both patients with HCV genotype 1a infection with baseline RAVs who received 16 or 18 weeks of EBR/GZR and ribavirin achieved SVR12," the researchers noted. Elbasvir is an HCV NS5A inhibitor, and GZR is an HCV NS3/4A protease inhibitor. In 2016, the Food and Drug Administration approved them in combination (Zepatier) for chronic genotype 1 and genotype 4 HCV. Studies have confirmed the benefits of treating HCV even when patients have cirrhosis, but they can be challenging to treat, especially if they have already failed a regimen that included a direct-acting antiviral agent, the investigators noted.

Studies have confirmed the benefits of treating HCV even when patients have cirrhosis, but they can be challenging to treat, especially if they have already failed a regimen that included a direct-acting antiviral agent.

To explore the efficacy of EBR/GZR in compensated, Child-Pugh A cirrhosis, they studied 402 such patients with HCV genotype 1, 4, or 6 infections whose baseline HCV RNA level exceeded 10,000 IU. Patients had participated in one of six phase II/III clinical trials and had received EBR/GZR 50 mg/100 mg once daily for 12-18 weeks, with or

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FROM THE AGA JOURNALS

Study estimates prevalence of pediatric celiac disease

BY AMY KARON
Frontline Medical News

By age 15 years, 3.1% of adolescents in Denver developed celiac disease, and another 2% developed a lesser degree of celiac disease autoimmunity, according to a 20-year prospective longitudinal study.

Watch this story's Video Insights at gastro.org/journals-and-publications/video-insights.

"Although more than 5% of children may experience a period of celiac disease autoimmunity [CDA], not all develop celiac disease [CD] or require gluten-free diets," Edwin Liu, MD, of University of Colorado School of Medicine and Children's Hospital Colorado (Aurora), wrote with his associates in the May issue of Gastroenterology (doi: 10.1053/j.gastro.2017.02.002). Most celiac autoimmunity probably develops before age 10, "which informs future efforts for universal screening," they added.

About 40% of the general population has the HLA-DQ2 or DQ8 risk genotypes for celiac disease, but little is known about rates of celiac disease among children in the United States, the researchers said. To help fill this gap, they analyzed celiac-risk HLA genotypes for 31,766 infants born between 1993 and 2004 from the Diabetes Autoimmunity Study in the Young. The 1,339 children with HLA risk genotypes were followed for up to 20 years.

By age 15 years, 66 of these children (4.9%) had developed tissue transglutaminase autoantibodies (tTGA) consistent with CDA, and also met criteria for CD, the researchers said. Another 46 (3.4%) children developed only CDA, of whom 46% experienced spontaneous resolution of tTGA seropositivity without treatment. By using genotype-specific risk weighting for population frequencies of HLA, the researchers estimated that 2.4% of the general population of Denver had CDA by age 5 years, 4.3% had CDA by age 10 years, and 5.1% had CDA by age 15 years. Estimated rates of CD were 1.6%, 2.8%, and 3.1%, respectively.

These findings suggest a significant rise in the incidence of CD compared with historical estimates in the United States, and reflect recent studies "using different approaches in North America," the researchers said. Reasons for the "dramatic increase" are unknown, but environmental causes seem likely, especially given the absence of identified genetic differences and marked changes in the prevalence of CD during the past 2 decades, they added.

Several other reports have documented fluctuating and transient tTGA antibodies in children, the researchers noted. Awareness of transient CD autoantibodies might limit public acceptance of universal screening programs for CD, they said. "Continued long-term follow-up will identify whether the autoimmunity in these subjects truly abates and tolerance develops, or if CDA will recur in time, possibly in response to additional stimulating events," they added. "At present, low positive tTGA results should be interpreted with caution, and do not necessarily indicate need for biopsy or for treatment."

The study did not include the DR5/DR7 risk genotype, which accounts for less than 5% of CD cases. The study also did not account for the estimated 2.5% of the general population that has DR3/DR7, which can be considered high risk, the researchers said. Thus, the study is conservative and might underestimate the real incidence of CD or CDA, they added.

The National Institutes of Health provided funding. The investigators reported having no conflicts of interest.

ginews@gastro.org

This study calls into question the incidence of celiac disease in the modern pediatric population and, by extension, future prevalence in adults. This is a unique prospective cohort study that followed children over a decade and a half and estimated a cumulative incidence of celiac disease of 3.1% by age 15. In sharp contrast, previous retrospective population-based studies estimated a prevalence of approximately 0.75%-1% in adult and pediatric populations. A recent publication by the United States Preventive Services Task Force used the previously accepted prevalence estimates to recommend against routine screening for celiac disease in the asymptomatic general population as well as targeted screening in those at higher risk. Increases in disease incidence as reported by the current study may call these recommendations into question, particularly in young children where cumulative incidence was high and potential for treatment benefit is substantial.


DR. ADAMS

The etiology of this increased incidence of celiac disease is unknown but strongly felt to be environmental. Two large prospective trials performed in Europe did not find infant feeding patterns to be a risk factor for development of celiac disease. Current theories include the amount of gluten ingestion, the role of early childhood infection and antibiotic exposure, and alterations in the gut microbiome. Future research in this area is crucial as we continue to experience and develop strategies to deal with this increasing incidence of celiac disease in our population.

Dawn Wiese Adams, MD, MS, is assistant professor, director of celiac clinic, in the department of gastroenterology, hepatology, and nutrition, Vanderbilt University Medical Center, Nashville, Tenn. She has no conflicts of interest.

Continued from previous page

without ribavirin (800-1,400 mg/day based on body weight). Treatment-naive patients received 12 weeks of treatment, while treatment-experienced patients received 12, 16, or 18 weeks of treatment.

Twelve weeks of ribavirin did not boost SVR for either treatment-naive (90%) or treatment-experienced (91%) patients, the researchers said. However, all 49 treatment-experienced patients who received EBR/GZR plus ribavirin for 16 or 18 weeks achieved SVR12, compared to 94% of patients who received EBR/GZR without ribavirin for 16 or 18 weeks.

Virologic failure was more common with HCV genotype 1a infections than with genotype 1b or 4 infection, especially if patients previously had not responded to interferon, the researchers noted. Eight of 11 (73%) patients with HCV genotype 1a infection and baseline NS5A RAVs achieved SVR12, compared with 98% of GT1a-infected patients without RAVs at baseline. But EBR/GZR was effective in various other subgroups, including patients with less than 100,000 platelets per microL, serum albumin below 3.5 g/dL, and FibroScan scores below 25 kPa. These findings suggest that EBR/GZR remains effective in patients with advanced compensated cirrhosis, the investigators said.

Most patients tolerated therapy, but six stopped treatment because of adverse events, including one episode of severe, possibly treatment-related abdominal pain. Also, four patients had late, asymptomatic rises in alanine aminotransferase (ALT) after first normalizing on treatment, and one patient stopped treatment because of grade 4 ALT elevation with eosinophilia. "There were no decompensation events in this generally healthy cirrhotic population, and no other evidence of declining liver function while on treatment," the researchers added.

The integrated analysis was not prespecified, nor was it powered to compare outcomes between treatment arms. Only three patients had genotype 6 infection, and all were treatment experienced. Only 23 patients had genotype 4 infection. Also, most patients had well-compensated cirrhosis. Finally, the trials varied in terms of how they defined cirrhosis, the investigators noted.

Merck, which funded the study, makes elbasvir and grazoprevir. The investigators acknowledged medical writing and editorial assistance from ApotheCom, which Merck funded. Dr. Jacobson disclosed consulting relationships and grant funding from Merck, AbbVie, Bristol-Myers Squibb, Gilead, Intercept, Janssen, and Trek.

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FROM THE AGA JOURNALS

Psyllium cut frequency of abdominal pain in IBS

BY AMY KARON
Frontline Medical News

Consuming psyllium fiber significantly reduced the frequency, but not the severity, of abdominal pain in children with irritable bowel syndrome in a randomized, double-blind, placebo-controlled trial reported in the May issue of Clinical Gastroenterology and Hepatology (2016 Nov;14[11]:1667).

Psyllium therapy did not reduce the self-reported severity of abdominal pain, Robert J. Shulman, MD, of Baylor College of Medicine in Houston reported with his associates in Clinical Gastroenterology and Hepatology. Psyllium was associated with shifts in intestinal microbiota, compared with baseline, although the changes did not reach statistical significance when compared with placebo, the researchers added. "Further studies are needed to investigate the potential mechanism whereby psyllium decreases abdominal pain frequency in children with irritable bowel syndrome [IBS]," they wrote.

IBS affects up to 20% of school-aged children. Consuming psyllium is thought to improve abdominal pain and stooling symptoms in adults with IBS, but data are inconclusive, and few randomized trials have evaluated fiber in childhood IBS. Therefore, the investigators randomly assigned 103 children (average age, 13 years; standard deviation, 3 years) with IBS who had responded inadequately to an 8-day carbohydrate elimination diet to receive a single daily dose of either psyllium or placebo maltodextrin for 6 weeks. Children aged 7-11 years received 6 g of fiber, while those aged 12-18 years received 12 g of fiber. Patients filled out a daily pain and stool diary during a 2-week baseline assessment period and again during the final 2 weeks of the trial. They also underwent breath hydrogen and methane testing, gut permeability testing, and a stool microbiota assessment during the final weekend of treatment.

At baseline, the trial arms resembled each other in terms of frequency and severity of abdominal pain, psychological characteristics, percentage of normal stools, baseline hydrogen production, and gastrointestinal permeability, the researchers said. During the final 2 weeks of treatment, the psyllium arm reported an average of 8.2 (standard deviation, 1.2) fewer episodes of abdominal pain, compared with baseline, while the control arm reported a mean reduction of 4.1 (SD, 1.3) episodes of abdominal pain ($P = .03$). At the end of treatment, the arms did not significantly differ in percentage of breath hydrogen or methane production, gastrointestinal permeability, or percentage of normal stools or diarrhea. However, controls had a significantly greater reduction in constipation compared with the psyllium group ($P = .048$).

Stool microbiome assessments of 33 children revealed a trend toward a greater increase in *Bacteroidetes* and a greater decrease in *Firmicutes* bacteria in the fiber group, compared with the control group ($P = .068$). The fiber group was also "marginally enriched" in bacteria of class Bacteroidia, while the placebo group was enriched in bacteria of class Clostridia ($P = .094$). However, the groups did not differ at narrower taxonomic levels, the researchers said. A larger sample size might have facilitated better detection of differences between groups, such as in breath hydrogen production or interactions between abdominal pain and psychological symptoms, they added.

The study was supported in part by the National Institutes of Health, the Daffy's Foundation, and the USDA/ARS. The investigators reported having no conflicts of interest.

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Occult cancers contribute to GI bleeding with anticoagulants

BY AMY KARON
Frontline Medical News

Occult cancers accounted for 1 in about every 12 major gastrointestinal bleeding events among patients taking warfarin or dabigatran for atrial fibrillation, according to a retrospective analysis of data from a randomized prospective trial reported in the May issue of Clinical Gastroenterology and Hepatology (doi: org/10.1016/j.cgh.2016.10.011).

These bleeding events caused similarly significant morbidity among patients taking either drug, Kathryn F. Flack, MD, of Icahn School of Medicine at Mount Sinai in New York and her associates wrote. "Patients bleeding from cancer required a mean of approximately 10 nights in the hospital, and approximately one-fourth required intensive care, but 0 of 44 died as a direct result of the bleeding," the researchers reported. They hoped the specific dabigatran reversal agent, idarucizumab, will improve bleeding outcomes in patients receiving dabigatran.

Major GI bleeding (MGIB) is the first sign of occult malignancy in certain patients receiving anticoagulation therapy. Starting an anticoagulant is a type of "stress test" that can reveal an occult cancer, the researchers said. Although dabigatran etexilate is generally safe and effective, a twice-daily, 150-mg dose of this direct oral anticoagulant slightly increased MGIB, compared with a lower dose in the international, multicenter RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial (N Engl J Med. 2009;361:1139-51).

Unlike warfarin, dabigatran therapy places active anticoagulant within the luminal GI, which "might promote bleeding from friable gastrointestinal cancers," the investigators noted. To explore this possibility, they evaluated 546 unique MGIB events among RE-LY patients.

Medical chart reviews identified 44 (8.1%) MGIB events resulting from occult GI cancers. Cancer accounted for similar proportions of MGIB among warfarin and dabigatran recipients. Nearly all cancers were colorectal or gastric, except for one case each of ampullary cancer, renal-cell carcinoma, and melanoma that had metastasized to the GI tract. Colorectal cancer accounted for 80% of cancer-related MGIB overall, including 88% in the dabiga-

Continued on page 14

Dr. Flack and her colleagues should be congratulated for providing important data as they reviewed 546 major GI bleeding events from a large randomized prospective trial of long-term anticoagulation in subjects with AF. They found that 1 in every 12 major GI bleeding events in patients on warfarin or dabigatran was associated with an occult cancer; colorectal cancer being the most common.

How will these results help us in clinical practice? First, when faced with GI bleeding in AF subjects on anticoagulants, a proactive diagnostic approach is needed for the search for a potential luminal GI malignancy; whether screening for GI malignancy before initiating anticoagulants is beneficial requires prospective studies with cost analysis. Second, cancer-related GI bleeding in dabigatran users occurs earlier than noncancer-related bleeding. Given that a fraction of GI bleeding events were not investigated, one cannot exclude the possibility of undiagnosed luminal GI cancers in the comparator group. Third, cancer-related bleeding is associated with prolonged hospital stay. We should seize the opportunity to study the effects of this double-edged sword; anticoagulants may help us reveal occult malignancy, but more importantly, we need to determine whether dabigatran-reversal agent idarucizumab can improve bleeding outcomes in patients on dabigatran presenting with cancer-related bleeding.

DR. NG

Siew C. Ng, MD, PhD, AGAF, is professor at the department of medicine and therapeutics, Institute of Digestive Disease, Chinese University of Hong Kong. She has no conflicts of interest.

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Aggressive HCC in males traced to higher serotonin

BY MARY ANN MOON
Frontline Medical News

The greater frequency and aggressiveness of hepatocellular carcinoma (HCC) in men than in women might be attributable to greater synthesis and accumulation of serotonin in males, according to a report published in Cellular and Molecular Gastroenterology and Hepatology (2017 May. doi: 10.1016/j.jcmgh.2017.01.002).

HCC is nearly five times more common in men than in women, and several molecular studies "have shown a more robust and active HCC tumor microenvironment" in men as well. For example, the density of infiltrating, tumor-associated macrophages is higher among males in a mouse model of the cancer, and human men have substantially higher amounts of intratumoral cluster-of-differentiation cells and neutrophils that indicate a poor prognosis, said Qiqi Yang, PhD, of the department of biological sciences at the National University of Singapore, and her associates.

The investigators developed several zebrafish models of HCC in which the cancer could be induced by transgenic expression of an oncogene in the animals' hepatocytes. These models "allow the oncogene to be activated at a given and controlled timing in both sexes, providing an excellent platform to study the sex disparity in HCC initiation and progression," they noted.

They also confirmed the zebrafish findings in human lab studies by analyzing tissue samples from 5

Continued from page 12

tran group and 50% in the warfarin group ($P = .02$). Conversely, warfarin recipients had more MGIB associated with gastric cancer (50%) than did those on dabigatran (2.9%; $P = .001$).

Short-term outcomes of MGIB associated with cancer did not vary by anticoagulant, the investigators said. There were no deaths, but 2 (4.5%) MGIB events required emergency endoscopic treatment, 1 (2.3%) required emergency surgery, and 33 (75%) required at least one red blood-cell transfusion. Compared with patients whose MGIB was unrelated to cancer, those with cancer were more likely to bleed for more than 7 days (27.3% vs. 63.6%; P less than .001). Patients with occult cancer also developed MGIB sooner after starting anticoagulation (223 vs. 343 days; $P = .003$), but time to bleeding did not vary by type of anticoagulant.

The RE-LY trial was sponsored by Boehringer Ingelheim. Dr. Flack reported no conflicts. James Aisenberg, MD, AGAF, disclosed advisory board and consulting relationships with Boehringer Ingelheim and Portola Pharmaceuticals. Five other coinvestigators disclosed ties to several pharmaceutical companies, and two coinvestigators reported employment with Boehringer Ingelheim.

normal livers, 7 inflamed livers, 16 cirrhotic livers, and 30 livers affected with HCC.

The investigators found an increased level of serotonin production in male, compared with female, livers. They demonstrated that serotonin was necessary for the survival of hepatic stellate cells, which also are more abundant in males than in females and have recently been shown to promote tumorigenesis. Serotonin also was crucial for activating hepatic stellate cells during HCC carcinogenesis.

In addition, serotonin levels were significantly elevated in inflamed, cirrhotic, and cancerous livers, compared with normal livers, among men but not among women. "This is in line with the prevailing knowledge that men have a significantly higher rate of serotonin synthesis than do women," Dr. Yang and her associates said.

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Serotonin is a small molecule neurotransmitter with diverse functions such as modulation of mood, appetite, wound healing, gastrointestinal motility, and blood coagulation. It was shown that serotonin can promote liver regeneration in mice via a direct action on hepatocytes, the main building blocks of liver. However, other cell types such as liver stellate cells, the main liver fibrogenic cells, can also be influenced by serotonin. Serotonin action on liver stellate cells results in production of transforming growth factor–beta1 (TGF-beta1), a multifunctional cytokine. TGF-beta1 can then inhibit regeneration of hepatocytes and promote fibrosis. In a new study, scientists have shown that the same pathway is active during hepatic carcinogenesis and promotes development of cancer in a zebrafish model. They also discovered that hepatocytes can produce serotonin and increase TGF-beta1 synthesis in stellate cells. Interestingly, they uncovered a significant sexual dimorphism in both human and fish samples in components of this pathway (for example, more serotonin and TGF-beta1 in males). This study unravels underlying mechanisms of sex differences in liver cancer. Importantly, it can provide a therapeutic opportunity to treat human liver cancer by modulation of serotonin signaling. This approach is attractive since potent and selective pharmacologic agents for serotonin signaling are already available for other purposes such as modulation of gut motility or neurological disorders. Future studies using human cells or samples will pave the path toward clinical translation of these findings.

DR. EBRAHIMKHANI

Mo Ebrahimkhani, MD, is an assistant professor in the school of biological and health systems engineering, Arizona State University, Tempe. He has no conflicts of interest.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

AGA tools help GIs manage patients with obesity

Patients with obesity need a multidisciplinary approach to achieve a healthy weight. AGA understands the importance of embracing obesity as a chronic, relapsing disease and supports a multidisciplinary approach to the management of obesity led by gastroenterologists.

To watch
AGA Solutions to Successful Obesity Program Integration: Andres Acosta, MD, PhD, assistant professor in medicine, clinical enteric neuroscience translational and epidemiological research, division of gastroenterology and hepatology, Mayo Clinic, Rochester, MN, and Sarah Streett, MD, AGAF, clinical associate professor and director of IBD, Stanford (Calif.) University, discuss the AGA Obesity Guide and how GIs can begin to implement the program in their practices. Watch the on-demand webinar in the AGA Community resource library.

To read
POWER: Practice Guide on Obesity and Weight Management, Education and Resources: This practice guide on obesity and weight management will help you develop a multidisciplinary team and obesity care model for your practice.

Episode-of-Care Framework for the Management of Obesity: Moving toward high-value, high-quality care – AGA established an obesity episode-of-care model to develop a framework to support value-based management of patients with obesity, focusing on the provision of nonsurgical and endoscopic services.

These resources are available at www.gastro.org/obesity.

To discuss
Visit the AGA Community (community.gastro.org) to join the discussion on managing your patient with obesity.

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Silvia Affo, PhD
Columbia University
2017 AGA Research Scholar Award Recipient


DR. AFFO

"I am extremely grateful to be selected for this award. I would like to thank the AGA Research Foundation and foundation donors for their generous support. This award will help me to build a research program to better understand mechanisms that promote the growth of cholangiocarcinoma." – Dr. Affo will use this research funding to address the role of cancer-associated fibroblasts in cholangiocarcinoma using novel research tools.

Gary Wu, MD
University of Pennsylvania
2017 AGA-Dannon Gut Microbiome in Health Award

"I am deeply honored to be the recipient of this award. The resources provided by this award will allow us to investigate models for small molecule generation by the gut microbiota that influence the plasma metabolome of the host. These models will be particularly important to understand the manner by which diet serves as a substrate for the gut microbiota to produce metabolites that ultimately have an impact on human health." – Dr. Wu will use this research initiative grant to support his team's continued exploration into the microbiome, which will have tremendous impact on the future of health care.


DR. WU

Jose Saenz, MD, PhD
Washington University School of Medicine
2017 AGA–Gastric Cancer Foundation Research Scholar Award in Gastric Cancer


DR. SAENZ

"I am honored to be a recipient of this award. I would like to thank the AGA for their generous contribution that will fund a crucial transition in my career. I would equally like to thank the various mentors that have guided me through this process and have provided invaluable advice in pursuit of my goals. This award will provide support to further understand the host-microbial interactions that characterize *Helicobacter pylori*'s regional and glandular colonization of the stomach." – Dr. Saenz notes that this award represents a commitment to studying early events in the preneoplastic cascade toward gastric adenocarcinoma, one of the leading causes of cancer-related deaths worldwide.

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Quick quiz

Q1. A 58-year-old woman with genotype 1a hepatitis C virus presents for reevaluation. She is treatment naive and a recent transient elastography reveals stage 3 fibrosis. Her past medical history is notable for atrial fibrillation, hypertension, and dyslipidemia. Medications include amiodarone, lisinopril, and atorvastatin.

Which regimen should be used to treat this patient's hepatitis C?
A. Paritaprevir/ritonavir, dasabuvir, ombitasvir, and ribavirin
B. Sofosbuvir, ledipasvir
C. Sofosbuvir, simeprevir
D. Sofosbuvir, daclatasvir

Q2. A consult is requested for a 32-year-old woman who is 29 weeks pregnant and has presented to the emergency department with nausea, vomiting, and right upper–quadrant abdominal pain. She is afebrile, pulse 89, BP 160/105. On exam, she has mild to moderate epigastric and right upper–quadrant tenderness. Her labs are notable for WBCs 13.0 x 10^9/L, Hgb 8.9 g/dL, platelets 55,000 x 10^9/L, AST 145 U/L, total bilirubin 2.1 mg/dL; PT and PTT are normal, blood glucose is 110 mg/dL.

Which of the following do you recommend to confirm the diagnosis?
A. Bile acid level
B. Peripheral blood smear
C. Liver biopsy
D. Serum lipase
E. Right upper–quadrant ultrasound

The answers are on page 34.

Could the end of hepatitis be near?

Road map *from page 1*

and his colleagues estimate.

But the authors also concede that drastic changes to current health policy would be required to reach these goals. These include the adoption of "aggressive testing, diagnosis, treatment, and prevention methods, such as needle exchange."

They propose that the federal government seek a unique licensing arrangement with one or more manufacturers to bring down the notoriously high cost of direct-acting drugs used in hepatitis C, as a way of raising treatment rates. Currently, fewer than half the patients on Medicaid who are eligible for hepatitis C treatment receive it, and fewer than 1% of prisoners, who have high rates of infection.

Dr. Joseph Lim, AGAF, director of the viral hepatitis program at Yale University in New Haven, Conn., who was not involved in the National Academies report, called it helpful in the sense that "it casts a spotlight on something that those of us involved in the care of people with viral hepatitis have long known – which is that this is a national and global public health burden that has been under the radar and in the shadow of other important health priorities."

Both hepatitis B and C increase the risk of liver cancer and are associated with significant morbidity and mortality. Though approximately 4 million people in the United States are estimated to be infected with chronic hepatitis B (1.3 million) or C (2.7 million), these diseases account for less than 1% of the research budget at the National Institutes of Health, the report said. This compares unfavorably to funding for HIV, which affects about 1 million Americans.

As the report states, the tools to radically reduce hepatitis B and C deaths already exist. However, Dr. Lim cautioned in an interview, "the public health infrastructure to address viral hepatitis has been woefully inadequate." In the United States, he noted, most states receive federal funding for at most a single person in charge of viral hepatitis epidemiology. "The resources currently available are in no way adequate to achieve the very aggressive goals described in the report," he said.

The National Academies advise that the government purchase 'a license or assignment to the patent on a direct-acting antiviral drug, and use it only in those market segments where the government pays for treatment and access is now limited.'

Even among people with a known diagnosis of hepatitis B or C, only some receive confirmatory testing, Dr. Lim said. And of those with confirmed infections, "only a fraction are linked to care from the diagnosing clinician to a provider with the capacity to assess the state of liver disease and determine whether antiviral therapy is warranted." Finally, he said, "many patients continue to face barriers to curative therapy due to cost and restrictions by public and private payers."

Among the recommendations contained in the report is that unrestricted, mass treatment of hepatitis C infections be undertaken – regardless of disease stage. Currently, direct-acting antiviral agents remain costly and are poorly covered, notably by Medicaid. The National Academies advise that the government rectify this by purchasing "a license

Continued on following page

AGA GUIDELINE

Transient elastography in liver fibrosis: Most accurate

BY AMY KARON
Frontline Medical News

Vibration-controlled transient elastography (VCTE) can accurately diagnose cirrhosis in most patients with chronic liver disease, particularly those with chronic hepatitis B or C, states a new guideline from the AGA Institute, published in the May issue of Gastroenterology (doi: 10.1053/j.gastro.2017.03.017).

However, magnetic resonance elastography (MRE) is somewhat more accurate for detecting cirrhosis in nonalcoholic fatty liver disease, wrote Joseph K. Lim, MD, AGAF, of Yale University in New Haven, Conn., with his associates from the Clinical Guidelines Committee of the AGA. VCTE is convenient but performs unevenly in some liver conditions and is especially unreliable in patients with acute hepatitis, alcohol abuse, food intake within 2-3 hours, congestive heart failure, or extrahepatic cholestasis, the guideline notes. Yet, VCTE remains the most common imaging tool for diagnosing fibrosis in the United States, and the guideline addresses "focused, clinically relevant questions" to guide its use.

For chronic hepatitis C, MRE had 'poorer specificity with higher false-positive rates, suggesting poorer diagnostic performance,' compared with VCTE. Lower cost and lower point-of-care availability make VCTE 'an attractive solution compared to MRE.'

When possible, clinicians should use VCTE instead of noninvasive serum tests for cirrhosis in patients with chronic hepatitis C, the guideline asserts. In pooled analyses of 62 studies, VCTE detected about 89% of cirrhosis cases (95% confidence interval, 84%-92%), Fibrosis-4 test (FIB-4) detected 87% (95% CI, 74%-94%), and aspartate aminotransferase to platelet ratio index (APRI) detected 77% (95% CI, 73%-81%). The specificity of VCTE (91%) also equaled or exceeded that of FIB-4 (91%) or APRI (78%), the guideline noted.

For chronic hepatitis C, MRE had "poorer specificity with higher false-positive rates, suggesting poorer diagnostic performance," compared with VCTE. Lower cost and lower point-of-care availability make VCTE "an attractive solution compared to MRE," the guideline adds. It conditionally recommends VCTE cutoffs of 12.5 kPa for cirrhosis and 9.5 kPa for advanced (F3-F4) liver fibrosis after patients have a sustained virologic response to therapy. The 9.5-kPa cutoff would misclassify only 1% of low-risk patients and 7% of high-risk patients, but noncirrhotic patients (less than 9.5 kPa) may reasonably choose to continue specialty care if they prioritize avoiding "the small risk" of hepatocellular carcinoma over the "inconvenience and risks of continued laboratory and fibrosis testing."

For chronic hepatitis B, the guideline conditionally recommends VCTE with an 11.0-kPa cutoff over APRI or FIB-4. In a pooled analysis of 28 studies, VCTE detected cirrhosis with a sensitivity of 86% and a specificity of 85%, compared with 66% and 74%, respectively, for APRI, and 87% and 65%, respectively, for FIB-4. However, the overall diagnostic performance of VCTE resembled that of the serum tests, and clinicians should interpret VCTE in the context of other clinical cirrhosis data, the guideline states.

Among 17 studies of VCTE cutoffs

Continued on page 24

Continued from previous page

or assignment to the patent on a direct-acting antiviral drug, and use it only in those market segments where the government pays for treatment and access is now limited, such as Medicaid and prisons."

Dr. Lim called the licensing proposal "very novel and bold," but noted that there is no precedent in the United States for diseases such as hepatitis C. "If it could be done it would be an incredible model of government-pharma partnership for the public health good, and have a very significant impact."

Steven Flamm, MD, chief of the liver transplantation program at Northwestern University in Chicago, who like Dr. Lim was not involved in the creation of the report, said in an interview that it contained innovative ideas and helped underscore the fact that "hepatitis has been given short shrift. The National Institutes of Health and other agencies do not devote time and energy to this particular medical issue for reasons that are not completely clear."

But "the problem with these kinds of analyses," he said, "is that carrying them out is harder than making the recommendations."

Dr. Flamm echoed Dr. Lim's concerns about the practicability of implementing some of the recommendations in what he considers a resource-deprived health care environment for viral hepatitis.

"Is elimination possible or can you take a big bite out of it? The answer to that question is yes. We now have agents that can treat chronic viral hepatitis well, which we didn't have a few years ago."

Still, he emphasized, having the tools is only one part of the picture. Hepatitis C diagnostic tests have been available since the early 1990s. Yet, Dr. Flamm pointed out, fewer than half of patients have been diagnosed. "If the new [Centers for Disease Control and Prevention] screening guidelines gain traction, we will do better than that."

Dr. Flamm said that he considered the report's call for a unique government licensing agreement for hepatitis C drugs a tall order. The drugs are already heavily discounted by manufacturers in many cases, he said, yet remain unavailable to those in need of them. In Illinois, Dr. Flamm said, few Medicaid patients with confirmed hepatitis C are given the short-acting antivirals that have revolutionized treatment. "The vast majority have no access to the therapy at all," he said.

One of the report's strengths, he said, is in detailing innovative prevention strategies such as delivering and promoting hepatitis B vaccinations to adults through local pharmacies, after the model of influenza vaccinations, and also conducting needle exchanges through pharmacies for intravenous drug users, who are at high risk of contracting both hepatitis B and C.

"Many of these strategies are not very costly," he said. "The problem is you run into moral platitudes – to eliminate hepatitis, we will have to overcome that," Dr. Flamm said, something that cannot be taken for granted in the current political environment.

But even if the goals outlined in the report seem ambitious, its authors have done an important service in underscoring the burden of viral hepatitis and laying out how some barriers to prevention, diagnosis, and treatment might be broken, he said.

Viral hepatitis "is a big deal, and it does cost a tremendous amount of money," he added. "Everybody focuses on the therapeutic cost, but nobody focuses on the costs, direct and indirect, of all the sick people that are out there."

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AGA CLINICAL PRACTICE UPDATE

Expert Review: Recommendations on hepatitis C care after sustained virologic response

BY MARY ANN MOON
Frontline Medical News

The AGA Institute issued a clinical practice update for managing hepatitis C virus–infected patients who achieve a sustained virologic response after antiviral therapy, who still require ongoing care for their liver disease; it is published in the May issue of Gastroenterology (doi: org/10.1053/j.gastro.2017.03.018).

Even though direct-acting antiviral regimens have produced remarkably high sustained virologic response (SVR) rates and it appears that fewer than 1% of patients relapse, and even though liver fibrosis and cirrhosis may regress with this therapy, continued surveillance and even intervention may be needed "to reduce complications arising from liver damage that has already accrued by the time SVR was attained," said Ira M. Jacobson, MD, AGAF, chair of the department of medicine, Mount Sinai Beth Israel Medical Center, New York, and his associates.

"Of greatest concern is the ongoing risk of hepatocellular carcinoma," they noted. Dr. Jacobson and his associates at the AGA Institute reviewed the current literature and expert opinion to formulate 11 best-practice recommendations for managing this patient population. Among their recommendations:

All patients who achieve SVR must be counseled regarding factors that could further injure the liver and contribute to the progression of fibrosis, hepatic decompensation, or the development of hepatocellular carcinoma.

SVR should be confirmed by hepatitis C virus RNA testing at 12 weeks after completion of an all-oral direct-acting antiviral regimen, and routine confirmation after 48 weeks is also "prudent." Further testing for later virologic relapse is not supported by the available evidence. However, further periodic testing is advised for patients at risk for reinfection, such as those who continue to use IV drugs.

All patients with stage 3 or higher liver fibrosis or cirrhosis before achieving SVR should continue to be monitored by liver imaging (with or without serum alpha fetoprotein testing) twice a year "for an indefinite duration." At present, there is no evidence of a finite point beyond which the risk of hepatocellular carcinoma is reduced to the level of people who don't have a history of liver disease. And there have been documented cases of hepatocellular carcinoma developing more than 5 years after attaining SVR.

Regardless of SVR status, all patients with liver cirrhosis should undergo endoscopic screening for esophagogastric varices. If no varices or only small varices are detected, repeat endoscopy should be done 2-3 years after achieving SVR. If no varices are identified then, "cessation of further endoscopic screening may be considered on an individual patient basis if there are no risk factors for progressive cirrhosis."

Noninvasive assessment of fibrosis, such as liver elastography, may be considered on an individual basis after SVR is attained, to assess whether fibrosis has progressed or regressed or to guide clinical management.

All patients who achieve SVR must be counseled regarding factors that could further injure the liver and contribute to the progression of fibrosis, hepatic decompensation, or the development of hepatocellular carcinoma. These include alcohol consumption, fatty liver, diabetes, and potential toxins. If serum liver enzyme levels rise, all patients should be evaluated for possible liver injury.

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in hepatitis B, an 11.0-kPa threshold diagnosed cirrhosis with a sensitivity of 81% and a specificity of 83%. This cutoff would miss cirrhosis in less than 1% of low-risk patients and about 5% of high-risk patients and would yield false positives in 10%-15% of patients. Thus, its cutoff minimizes false negatives, reflecting "a judgment that the harm of missing cirrhosis is greater than the harm of over diagnosis," the authors write.

For chronic alcoholic liver disease, the AGA conditionally recommends VCTE with a cirrhosis cutoff of 12.5 kPa. In pooled analyses, this value had a sensitivity of 95% and a specificity of 71%. For suspected compensated cirrhosis, the guideline conditionally suggests a 19.5-kPa cutoff when assessing the need for esophagogastroduodenoscopy (EGD) to identify high-risk esophageal varices. Patients who fall below this cutoff can reasonably pursue screening endoscopy if they are concerned about the small risk of acute variceal hemorrhage, the guideline adds.

The guideline also conditionally recommends a 17-kPa cutoff to detect clinically significant portal hypertension in patients with suspected chronic liver disease who are undergoing elective nonhepatic surgeries. This cutoff will miss about 0.1% of very-low-risk patients, 0.8% of low-risk patients, and 7% of high-risk patients. Because the failure to detect portal hypertension contributes to operative morbidity and mortality, higher-risk patients might "reasonably" pursue screening endoscopy even if their kPa is below the cutoff, the guideline states.

The guideline made no recommendation about VCTE versus APRI or FIB-4 in adults with nonalcoholic fatty liver disease (NAFLD), citing "unacceptable bias" in 12 studies that excluded obese patients, used per-protocol rather than intention-to-diagnose analyses, and ignored "unsuccessful or inadequate" liver stiffness measurements, which are relatively common in NAFLD, the guideline notes. It conditionally recommends MRE over VCTE in high-risk adults with NAFLD, including those who are older, diabetic, or obese (especially with central adiposity) or who have alanine levels more than twice the upper limit of normal. However, it cites insufficient evidence to extend this recommendation to low-risk patients who have only imaging evidence of fatty liver.

'Additional studies are needed to further define the role of VCTE, MRE, and emerging diagnostic studies in the assessment of liver fibrosis, for which a significant unmet medical need remains, particularly in conditions such as NAFLD/[nonalcoholic steatohepatitis].'

Overall, the guideline focuses on "routine clinical management issues, and [does] not address comparisons with proprietary serum fibrosis assays, other emerging imaging-based fibrosis assessment techniques, or combinations of more than one noninvasive fibrosis test," the authors note. They also limited VCTE cutoffs to single thresholds that prioritized sensitivity over specificity. "Additional studies are needed to further define the role of VCTE, MRE, and emerging diagnostic studies in the assessment of liver fibrosis, for which a significant unmet medical need remains, particularly in conditions such as NAFLD/[nonalcoholic steatohepatitis]," they add. "In particular, defining the implications for serial liver stiffness measurements over time on management decisions is of great interest."

Dr. Muir has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead, and Merck. Dr. Lim has served as a consultant for Bristol-Myers Squibb, Gilead, Merck, and Boehringer Ingelheim. Dr. Flamm has served as a consultant or received research support from Gilead, Bristol-Myers Squibb, AbbVie, Salix Pharmaceuticals, and Intercept Pharmaceuticals. Dr. Dieterich has presented lectures for Gilead and Merck products. The rest of the authors disclosed no conflicts related to the content of this guideline.

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Obesity at issue

Bariatric *from page 1*

ric surgery is already being used in her center to avoid a second liver transplant in obese patients who are unable to lose sufficient weight to prevent progressive NAFLD after a first transplant.

The emphasis Dr. Ayloo placed on the role of bariatric surgery in preventing progression of NAFLD to nonalcoholic steatohepatitis and the inflammatory process that leads to fibrosis, cirrhosis, and liver decompensation was drawn from her interest in these two fields. However, she did not ignore the potential of protection from obesity control for other diseases.

"We have a couple of decades of experience that has been published [with bariatric surgery], and this has shown that it maintains weight loss long term, it improves all the obesity-associated comorbidities, and it is cost effective," Dr. Ayloo said. Now with long-term follow-up, "all of the studies are showing that bariatric surgery improves survival."

Although most of the survival data have been generated by retrospective cohort studies, Dr. Ayloo cited nine sets of data showing odds ratios associating bariatric surgery with up to a 90% reduction in death over periods of up to 10 years of follow-up. In a summary slide presented by Dr. Ayloo, the estimated mortality benefit over 5 years was listed as 85%. The same summary slide listed large improvements in relevant measures of morbidity for more than 10 organ systems, such as improvement or resolution of dyslipidemia and hypertension, improvement or resolution of asthma and other diseases of the respiratory system, and resolution or improvement of gastroesophageal reflux disease and other diseases of the gastrointestinal system.

Specific to the liver, these benefits included a nearly 40% reduction in liver inflammation and 20% reduction in fibrosis. According to Dr. Ayloo, who noted that NAFLD is expected to overtake hepatitis C virus as the No. 1 cause of liver transplant within the next 5 years, these data are important for drawing attention to bariatric surgery as a strategy to control liver disease. She suggested that there is a need to create a tighter link between efforts to treat morbid obesity and advanced liver disease.

"There is an established literature showing that, if somebody is morbidly obese, the rate of liver transplant is lower than when compared to patients with normal weight," Dr. Ayloo said. "There is a call out in the transplant community that we need to address this."

Because of the strong relationship between obesity and NAFLD, a systematic approach is needed to consider liver disease in obese patients and obesity in patients with liver disease, she said. The close relationship is relevant when planning interventions for either. Liver disease should be assessed prior to bariatric surgery regardless of the indication and then monitored closely as part of postoperative care, she said.

Dr. Ayloo identified weight control as an essential part of post-transplant care to prevent hepatic fat deposition that threatens transplant-free survival.

Global Academy and this news organization are owned by the same company. Dr. Ayloo reports no relevant financial relationships.

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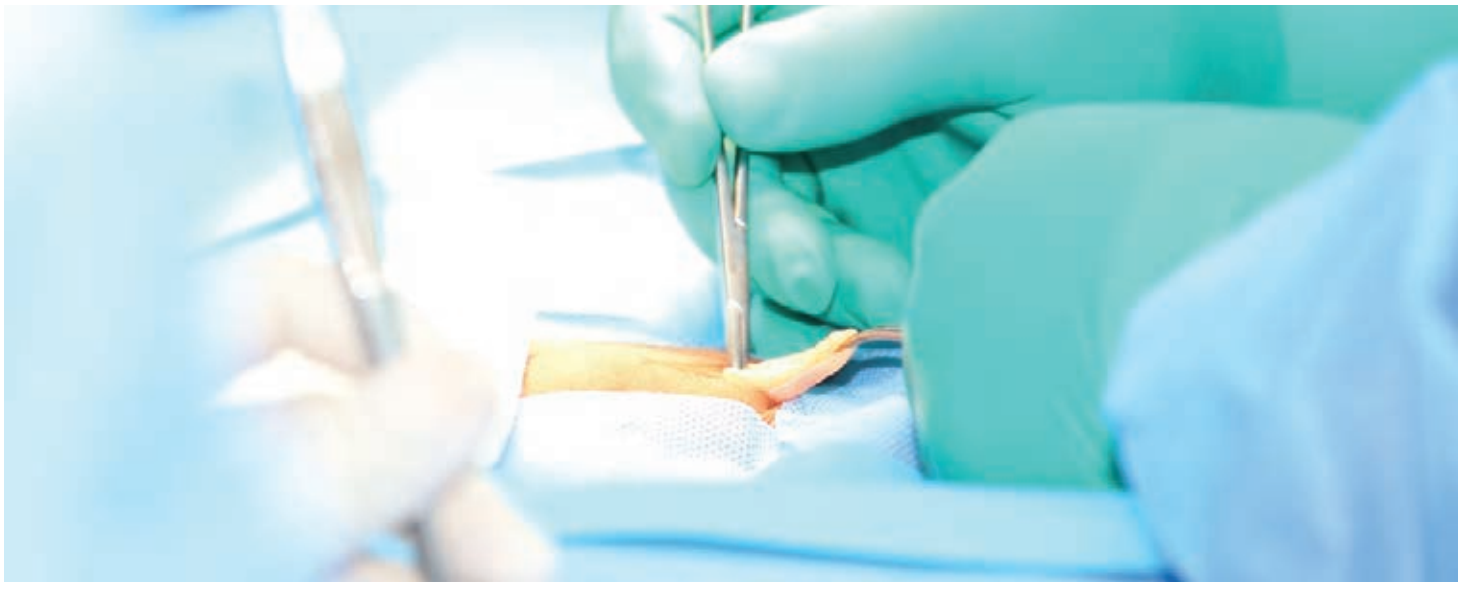
Mesh at ostomy site prevents parastomal hernia

BY MARY ANN MOON
Frontline Medical News



CASTILLODOMINICI/THINKSTOCK

For patients undergoing elective permanent colostomy, prophylactic augmentation of the abdominal wall using mesh at the ostomy site prevents the development of parastomal hernia, according to a report published in the April issue of Annals of Surgery.

The incidence of parastomal hernia is expected to rise because of the increasing number of cancer patients surviving with a colostomy, and the rising number of obese patients who have increased tension on the abdominal wall because of their elevated intra-abdominal pressure and larger abdominal radius. Researchers in the Netherlands performed a prospective randomized study, the PREVENT trial, to assess whether augmenting the abdominal wall at the ostomy site, using a lightweight mesh, would be safe, feasible, and effective at preventing parastomal hernia. They reported their findings after 1 year of follow-up; the study will continue until longer-term results are available at 5 years.

A total of 133 adults (aged 18-85 years) scheduled for permanent end-colostomy were enrolled in the study at 11 teaching hospitals and three university medical centers across the Netherlands during a 3-year period. They were randomly assigned to receive prophylactic reinforcing mesh at the stoma site (67 patients in the intervention group) or conventional stoma formation (66 patients in the control group), said Henk-Thijs Brandsma, MD, of Canisius Wilhelmina Hospital, Nijmegen, the Netherlands, and his associates.

In the intervention group, a retromuscular space was created to accommodate the mesh by dissecting the muscle from the posterior fascia or peritoneum to the lateral border via a median laparotomy. An incision was made in the center of the mesh to allow passage of the colon, and the mesh was placed on the posterior rectus sheath and anchored laterally with two absorbable sutures. "On the medial side, the mesh was incorporated in the running suture closing the fascia, thus preventing contact between the mesh and the viscera," the investigators said (Ann Surg. 2017;265:663-9).

The primary end point – the incidence of parastomal hernia at 1 year – occurred in 3 patients (4.5%) in the intervention group and 16 (24.2%) in the control group, a significant difference. There were no mesh-related complications such as infection, strictures, or adhesions. "The majority of the parastomal hernias that required surgical repair were in the control group, which supports the concept that if a hernia develops in a patient with mesh, it is smaller and less likely to cause complaints," Dr. Brandsma and his associates said.

Significantly fewer patients in the mesh group (9%) than in the control group (21%) reported stoma-related complaints such as pain, leakage, and skin problems. Scores on measures of quality of life and pain severity were no different between the two study groups.

"Prophylactic augmentation of the abdominal wall with a retromuscular polypropylene mesh at the ostomy site is a safe and feasible procedure with no adverse events. It significantly reduces the incidence of parastomal hernia," the investigators concluded.

This study was supported by Canisius Wilhelmina Hospital's surgery research fund, the Netherlands Organization for Health Research and Development, and Covidien/Medtronic. Dr. Brandsma and his associates reported having no relevant financial disclosures.

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Viral trigger studied

Celiac *from page 1*

Some epidemiologic evidence suggested that adenovirus, enteroviruses, hepatitis C virus, and rotavirus may be celiac disease triggers, but there was little experimental evidence to support these ideas.

The researchers decided to investigate reoviruses. They often infect humans, commonly in early childhood when gluten usually is first introduced. They also infect humans and mice similarly, allowing a more straightforward comparison between human and mouse studies than would be possible in other virus types.

The researchers created an engineered virus made from two reovirus strains, T1L and T3D, which naturally reassort in human hosts. T1L infects the intestine, while T3D does not. The new strain, T3D-RV, retains most of the characteristics of T3D but can also infect the intestine.

The researchers then conducted mouse studies and showed that both T1L and T3D-RV affect immune responses to dietary antigens at the inductive and effector sites of oral tolerance. However, the original T1L strain caused more changes in gene transcription, both in the number of genes and the intensity of transcription level. This suggested that T1L might uniquely alter immunogenic responses to dietary antigens.

A further test in mice showed that T1L also prompted a proinflammatory response in dendritic cells that take up ovalbumin, but T3D-RV did not. Furthermore, T1L interfered with induction of peripheral tolerance to oral ovalbumin, and T3D-RV did not.

With these data in hand, the researchers turned to human subjects. They compared 73 healthy controls to 160 patients with celiac disease who were on a gluten-free diet. Celiac disease patients had higher mean antireovirus antibody titers, though the result fell short of statistical significance ($P = .06$), and subjects with celiac disease were over-represented among subjects who had antireovirus titers above the median value.

"You can have two viruses of the same family infecting the intestine in the same way, inducing protective immunity, and being cleared, but only one sets the stage for disease. Finally, using these two viruses allows [us] to dissociate protective immunity from immunopathology. Only the virus that has the capacity to enter the site where dietary proteins are seen by the immune system can trigger disease," said Bana Jabri, MD, PhD, professor of medicine at the University of Chicago.

Reovirus is unlikely to be the only, otherwise harmless, virus that could prompt wayward immune responses. The research points the way to the identification of viruses linked to celiac disease and other autoimmune diseases and could inform vaccine strategies to prevent such conditions.

The study received funding from the National Institutes of Health and the University of Chicago. No conflict of interest information was disclosed in the article.

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THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

FDA approves first home genetic health risk test

BY ELI ZIMMERMAN
Frontline Medical News

The Food and Drug Administration authorized 23andMe's Personal Genome Service Genetic Health Risk (GHR) test, the first direct-to-consumer genetic screening test, according to a press release on Thursday, April 6.

FDA officials expect the product, which tests individuals for possible genetic predisposition for 10 diseases including Parkinson's, late-onset Alzheimer's, alpha-1-antitrypsin deficiency, celiac disease, and hereditary hemochromatosis, to spur patients to consult with their physicians and make more informed lifestyle decisions.

The GHR test works by testing DNA from an individual's saliva for more than 500,000 genetic variants. FDA officials warn that, while the test gives users a better idea of the odds of one of these diseases manifesting, it is not meant to be used as a diagnostic tool.

"Consumers can now have direct access to certain genetic risk information," said Jeffrey Shuren, MD, director of the FDA's Center for Devices and Radiological Health in the release. "But it is important that people understand that genetic risk is just one piece of the bigger puzzle, it does not mean they will or won't ultimately develop a disease."

The FDA has exempted all further GHR tests developed by 23andMe from premarket review, noting future GHR tests developed by other makers, excluding those used for diagnostic purposes, may also achieve this exemption after submitting their first premarket review.

For the full details, see the original announcement.

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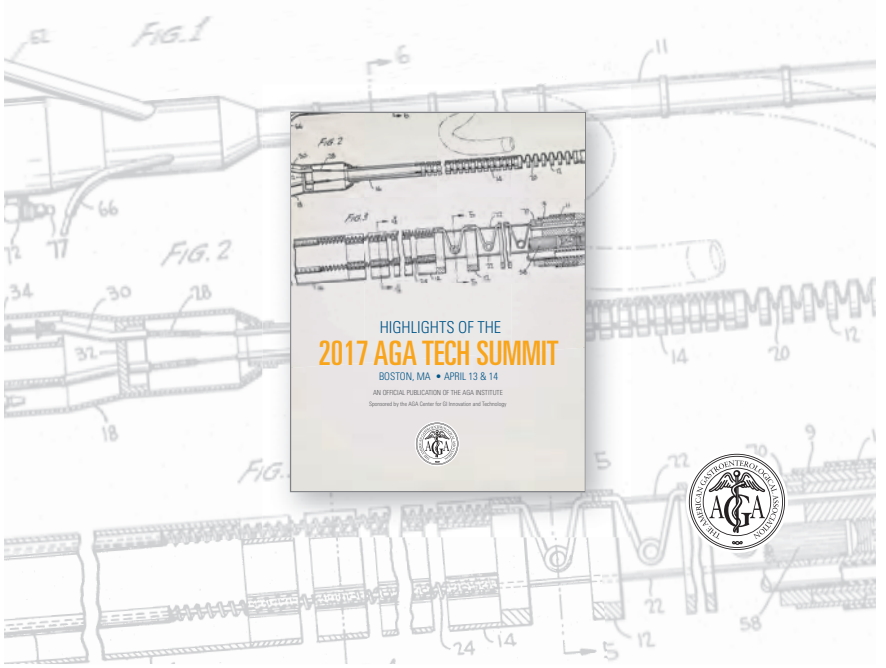
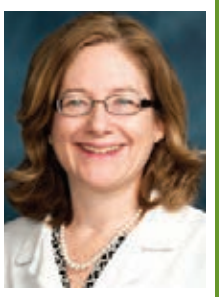


PERSPECTIVE

DTC genetic health risk tests: Beware



Clinicians should be aware that 23andMe was previously issued a warning by the FDA preventing them from including information about health risks on these DTC test reports. The FDA's authorization is not an endorsement of the validity or clinical utility of DTC health risk tests, which simply analyze whether an individual's DNA carries a genetic variant associated with "increased" risk for the condition in question. In fact, the American College of Medical Genetics warns that DTC genetic tests, have the potential to be misleading for both clinicians and patients, resulting in unnecessary worry and/or additional testing. As more consumers partake in "recreational genomic testing" clinicians should understand the limitations of DTC genetic tests and should be prepared to discuss with patients why these should not supersede clinical diagnostic evaluations.

Elena M. Stoffel, MD, MPH, is a gastroenterologist, assistant professor of internal medicine and director of the cancer genetics clinic at the University of Michigan. She has no disclosures.

DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz answers

Q1: Answer: A
The Food and Drug Administration issued a postmarketing warning about potential for interaction between sofosbuvir and amiodarone. Nine patients taking sofosbuvir (with other antiviral agents) and amiodarone developed significant bradycardia. Seven patients were on concomitant beta-blockade. One patient died of cardiac arrest while three others required pacemaker placement. Two-thirds of the events occurred within 24 hours of coadministration while the other third occurred within 12 days. Three patients had recurrence of bradycardia with rechallenge of sofosbuvir treatment while on amiodarone. Amiodarone is considered an absolute contraindication to the use of a sofosbuvir-containing regimen. The sofosbuvir-containing regimens listed are endorsed by the AASLD/IDSA joint guidelines for treatment of genotype 1a hepatitis C, as long as the patient is not on amiodarone, although the combination of sofosbuvir and daclatasvir is not FDA approved for genotype 1.

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Q2: Answer: B
Objective: Diagnose HELLP syndrome
Rationale: This patient's presentation and laboratory findings are consistent with HELLP syndrome – the syndrome of hemolysis, elevated liver enzymes, and low platelets. Patients with HELLP will have hypertension (BP above 140/90), thrombocytopenia to less than 100,000/mm^3, and aminotransferase levels above 70 U/L.

The diagnosis can be confirmed with an LDH (lactate dehydrogenase) greater than 600 U/L and microangiopathic hemolytic anemia on peripheral blood smear. On liver biopsy, HELLP is characterized by periportal or focal parenchyma necrosis with hyaline deposition of fibrin material in the sinusoids. However, liver biopsies are rarely performed in this setting as it likely will not change management (delivery of the fetus) and it exposes the mother and fetus to additional risks.

There is significant overlap between HELLP and acute fatty liver of pregnancy, although elevated prothrombin and partial thromboplastin time, severe hypoglycemia, and elevated creatinine are more common in acute fatty liver of pregnancy. Hypertension is more common in HELLP, and therefore this patient's presentation is more consistent with HELLP.

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Persistent diarrhea:
are there faster diagnostic pathways?*

Persistent diarrhea is a common condition associated with multiple etiologies, which can make it challenging to diagnose the underlying cause.[1,2] A new advancement that streamlines the diagnostic pathway could help healthcare providers consider condition-specific treatment early for their patients.

Current challenges

The differential diagnosis for persistent diarrhea is extensive.[1] It is also not uncommon for patients to have more than 1 potentially causative factor.[3] The etiology of persistent diarrhea can include numerous infectious causes, including parasites (eg, *Giardia* and *Cryptosporidium*) and bacteria (eg, *Escherichia coli*, *Shigella*, and *Campylobacter*), and viruses (eg, norovirus).[4] There are also multiple noninfectious causes, including inflammatory bowel disease (IBD), celiac disease, irritable bowel syndrome (IBS), and bile acid malabsorption (BAM), which may be more prevalent than previously believed.[4,5]

As a result, diagnosis of persistent diarrhea can be a slow process,[1,4] and some patients may suffer longer than necessary. Having to order multiple tests may also be inconvenient for both healthcare providers and patients.

Convenient all-in-one testing is now available

Now there is a stool and serum test that may help healthcare providers diagnose many common causes of persistent diarrhea all at 1 time for added convenience. The PROMETHEUS® IBcause™ Diagnostic Test helps physicians diagnose common causes of persistent diarrhea—including intestinal inflammation, celiac disease, IBS, multiple pathogens, and BAM.[1,4,6-9,**] IBcause can also help clinicians determine if a multifactorial gastrointestinal condition may be irritating the bowel and causing persistent diarrhea, something that could remain unrecognized with sequential testing or empiric treatment.[4]

Combines multiple stool and serum assays***

IBcause evaluates a unique combination of 20 stool and serum measures all at 1 time, which may help clinicians get to a diagnosis faster and a specific treatment plan sooner (compared to sequential testing and empiric treatment). It quickly helps identify both infectious and noninfectious causes of persistent diarrhea in 1 easy-to-order test that is convenient for both clinicians and their patients.

Addition of BAM assay provides a more complete view*

Bile acid diarrhea is common in patients who have ileal-specific Crohn's disease or have undergone ileal resection surgery.[10] Perhaps lesser known is that BAM may affect up to 50% of patients with unexplained persistent diarrhea.[10] BAM is also a condition that is often overlooked or is misdiagnosed as diarrhea-predominant irritable bowel syndrome (IBS-D).[5,11] Some have suggested that IBS-D patients who fail standard therapy should be evaluated for possible BAM. A challenge is that the standard test for measuring bile acid diarrhea (the selenium homocholic acid taurine test, or SeHCAT) is not readily available in the United States, thereby hindering proper diagnosis.[10]

IBcause features a proprietary assay for BAM that is not available elsewhere to test for elevated 7α-hydroxy-4-cholesten-3-one (7C4) plasma levels, which have been associated with BAM.[10]

IBcause represents an important advancement for IBS-D patients who have not had success with standard therapy and can now be evaluated for BAM.[10] In a study where serum 7C4 levels were measured in IBS-D patients (n = 26), IBS with constipation patients (IBS-C, n = 26), and healthy subjects (n = 26), the IBS-D patients had increased hepatic bile acid synthesis, and greater levels of excreted bile acid were detected in stools collected for over 2 days.[12]

Tests for 14 types of pathogens

IBcause allows clinicians to simultaneously test for multiple pathogens that may present concurrently in patients with persistent diarrhea, including 8 types of bacteria, 3 types of parasites, and 3 types of viruses. Due to advanced polymerase chain reaction (PCR)–based amplification, IBcause is faster and more sensitive than conventional culture-based stool-testing methods. Clinicians can use IBcause to rule out > 90% of acute diarrhea-causing agents, including bacterial toxins.[13-15]

Utilizing IBcause can help clinicians streamline the diagnostic pathway for patients who present with persistent diarrhea.* For more information, visit IBcause.com or call Prometheus Customer Services at **888-423-5227**, Option 1, for additional information.

A new way to streamline the diagnostic pathway for persistent diarrhea*

Learn more at IBcause.com

*Compared to sequential testing with standard workup for persistent diarrhea.

**IBcause is recommended for patients with ongoing diarrhea (which may be referred to as persistent or chronic).

***Assays can also be ordered separately and all results should be used in combination with other clinical findings.

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PPI-responsive EoE may be misnomer

BY TED BOSWORTH
Frontline Medical News

PHILADELPHIA – Eosinophilic esophagitis (EoE) responsive to a proton pump inhibitor (PPI) has been characterized as PPI-responsive esophageal eosinophilia (PPI-REE), but there is no compelling evidence that it is a distinct EoE subgroup, according to an expert who updated current thinking about this disease at Digestive Diseases: New Advances.


DR. SPECHLER

"Multivariate analyses have not identified any feature that distinguishes PPI-REE from EoE. Why? Because they are probably the same disorder," reported Stuart J. Spechler, MD, AGAF, codirector of the center for esophageal diseases at Baylor University Medical Center at Dallas.

The substantial response in EoE patients to PPI therapy, which is nearly 50% in some studies, has been a source of confusion. PPIs reduce gastric acid, but EoE is not an acid-related disease, according to Dr. Spechler. The picture is now becoming clearer with new evidence that PPIs do more. Dr. Spechler reviewed evidence that PPIs inhibit inflammatory cells, exert antioxidant properties, and decrease the inflammatory cytokine signaling that drives eosinophil activation and adhesion.

Although it is true that only a subset of EoE patients respond to PPIs, few therapies are effective for all patients in any disease Dr. Spechler observed. As an example, he noted that ulcerative colitis patients who respond to sulfasalazine are not subclassified as sulfasalazine-responsive ulcerative colitis.

"I do think the term PPI-REE should be retired, although I acknowledge that not everyone in this field is ready to agree," Dr. Spechler said at the meeting, held by Rutgers, the State University of New Jersey, and Global Academy for Medical Education. Global Academy and this news organization are owned by the same company.

The confusion regarding PPI responsiveness in EoE has been driven by the fact that acid control has been widely regarded as the only pertinent mechanism of action from PPIs. Although coexisting gastroesophageal reflux disease could explain symptom relief in some patients with EoE, no evidence of excess acid is found in many responders. Detailed evaluations of the PPI-REE subgroup relative to EOE overall emphasize this point, according to Dr. Spechler.

"Studies have shown that the clinical, endoscopic, histologic, and gene expression features of these two disorders are identical," he reported.

The lack of distinction is now easier to understand with a growing body of evidence that PPIs have acid-independent effects relevant to benefit in EoE, according to Dr. Spechler. Tracing the advances in understanding the pathogenesis in EoE since it was first described in 1978, Dr. Spechler explained that EoE is now understood to be an antigen-driven expression of food allergy related to up-regulation of the Th2 helper adaptive response. After briefly reviewing several potential anti-inflammatory effects of PPIs, Dr. Spechler focused on evidence that PPIs inhibit the adhesion molecule eotaxin-3.

Specifically, when squamous cells from EoE patients are exposed to the cytokine interleukin-4 (IL-4), "production of eotaxin-3 is increased dramatically but you can block that cytokine Th2 stimulation with [the PPI] omeprazole," said Dr. Spechler, citing published work by Edaire Cheng, MD, a researcher with whom he has collaborated at the University of Texas Southwestern Medical School, Dallas. This is a potentially important observation, because up-regulation of eotaxin-3 is considered a critical molecular event for the activation of eosinophils and their migration.

The relative importance of this specific mechanism for explaining the benefits of PPIs in EoE requires additional confirmation, but Dr. Spechler indicated that there is strong evidence of acid-independent effects from PPIs. In fact, in outlining an algorithm for treatment of EoE, he listed a trial of PPIs as a reasonable first choice.

"In my opinion, the major reason that we created an arbitrary distinction is this persistent notion that acid inhibition is the only possible therapeutic effect of PPIs," Dr. Spechler reported. "I hope I have convinced you otherwise."

In his brief update of EoE treatment in 2017, Dr. Spechler identified a trial of PPIs as first-line "simply because they work." However PPIs have been rendered even more attractive by the evidence of a plausible mechanism of action in EoE. Conversely, he cautioned that steroids are "just a band-aid" because "they cover up the allergy but the allergy remains." Ultimately, while PPIs are a reasonable first-line therapy to control symptoms, Dr. Spechler suggested that elimination diets are ultimately the best strategy for treating the underlying cause of EoE.

Dr. Spechler reported a financial relationship with Ironwood Pharmaceuticals.

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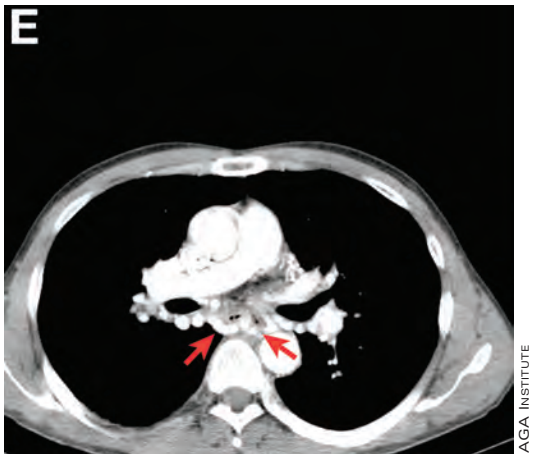
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" on page 6: Arteriovenous fistulas arising from the subclavian and coronary arteries

We performed aortography along with coronary angiography to find the feeding vessels for the vascular bundle. There was an arteriovenous fistula that arose from the left subclavian artery, ran over the left mediastinum with the complex plexus, and emptied into the venous system of the left thorax (Figure E). Multiple coronary artery fistulas originated in the left coronary artery, traversed the left and right mediastinum, and eventually emptied into the venous system of the mediastinum. The left anterior oblique view revealed a coronary artery fistula that arose from the distal right coronary artery and drained into the venous system of the thorax. In transthoracic echocardiography, the sizes of the left atrium and left ventricle were mildly dilated, but left ventricular systolic functions were preserved with an ejection fraction of 61%. We recommended surgery to the patient, but he refused invasive treatment. He will be followed with close observation.

A coronary artery fistula is usually of congenital origin, and connects a major coronary artery directly with the cardiac chamber, coronary sinus, superior vena cava, or pulmonary artery. However, its connection with a systemic venous system is extremely rare. Congenital subclavian arteriovenous fistulas are rare because they usually occur as a complication of previous trauma, percutaneous catheterization, or surgery.[1] Complications include "steal" from the adjacent myocardium causing myocardial ischemia, thrombosis/embolism, cardiac failure, atrial fibrillation, rupture, endocarditis/endarteritis, and arrhythmia.[2] Treatment options include close medical observation, surgical ligation, and catheter embolization.[3]



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THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

PRACTICE MANAGEMENT TOOLBOX: Integration of telemedicine into clinical gastroenterology and hepatology practice

BY RAYMOND K. CROSS, MD, MS, AGAF, AND SUNANDA KANE, MD

Two trends in health care delivery that will continue unabated are reimbursement pressure and increasing demand for our services. One approach currently being used by many health systems is telemedicine – care delivered remotely using some type of electronic communication. Telemedicine may allow us to provide specialty services remotely to primary care physicians or even patients. The University of Michigan inflammatory bowel disease program is piloting remote video conferencing, integrated within the electronic medical record system, to provide specialty gastrointestinal consultation directly to Crohn's and ulcerative colitis patients within their homes. The University of Michigan Health System has an office ready to arrange rapid teleconsultation for any provider. Payment for services has been secured from several payers after health system negotiations. In this month's column, two telemedicine experts review the state of the field, so you too can participate. Technology and payment mechanisms are now available.

John I. Allen, MD, MBA, AGAF
Editor in Chief

As defined by the American Telemedicine Association (ATA), telemedicine is the exchange of medical information from one site to another via electronic communication to improve a patient's clinical health status.[1] If we include care provided over the telephone via providers and nurses between office visits, telemedicine has been practiced for decades. A recent study from the University of Pittsburgh documented 32,667 phone calls from 3,118 patients with inflammatory bowel disease (IBD) in 2010. Seventy-five percent of these calls were related to patient concerns or were generated by the nurse because of changes in the treatment plan.[2] If these results are applied to a representative work week, busy IBD centers typically handle more than 100 phone calls per day.[3] Telemedicine in clinical practice has expanded to include a variety of modalities such as two-way video, email, or secure messaging through electronic medical records systems, smartphones, wireless tools, and other forms of telecommunication technology (see Figure 1).

First, it is almost universal that patients have access to a computer and/or cellular telephone. According to the Pew Research Center's Internet and American Life Project, as of May 2013, 91% of adults are using cell phones.[4] Second, despite advances in medical, endoscopic, and surgical treatment, many pa-

tients still have suboptimal outcomes. There are many reasons for this, including but not limited to nonadherence, poor patient education, inadequate monitoring of symptoms and side effects, concurrent psychiatric disease, comorbid medical conditions, low self-efficacy, and limited access to health care; these issues can be addressed, at least in part, by telemedicine. Finally, patients are also seeking more efficient and convenient ways to receive their care; including travel and wait times, an average office visit takes up to 2 hours.[5]

Telemedicine can be used to provide enhanced monitoring of patients between office visits, prompts for medication use and diagnostics, self-management plans, treatment of psychiatric disease, and education. Two-way videos between patients and providers can be used to expand access to a gastroenterologist for patients in remote areas and to providers with expertise in certain disciplines such as IBD, hepatology, and irritable bowel syndrome.

Enhanced monitoring and self-care through use of telemedicine technologies

Our group at the University of Maryland, Baltimore, has developed several systems to improve care as part of research protocols. Our first telemedicine system included a laptop computer and electronic weight scale connected telephonically to a server. Patients were asked questions about bowel symptoms, medication use, side effects, and body weight measurements. They also received educational messages. This system, IBD Home Automated Telemanagement (HAT), required installation in the patient's home by a technical team. Our preliminary results demonstrated that patients were very receptive of the technology.[6] In a small pilot study (n = 34), we demonstrated that 88% of patients were adherent to self-assessment during a period of 6 months. In addition, patients experienced a reduction in disease activity, improved quality of life, and increased disease state awareness.[7] In a small, randomized, controlled follow-up trial, we demonstrated that use of an ulcerative colitis (UC) telemanagement system (UC HAT) resulted in improved quality of life and decreased disease activity from baseline during 1 year compared with controls. The UC HAT system was enhanced to include self-care plans that were based on patient reporting of symptoms. Fewer participants completed the study in the UC HAT, compared with the control, group (56% vs. 72%).[8] We theorized that participant dropout was higher in the UC HAT group because of the requirement for a technician to visit the home to install or service the system. Hence, as part of a randomized controlled trial, our group has collaborated with the University of Pittsburgh and Vanderbilt University to assess a new telemedicine system that monitors patients by using text messaging.[9] Three hundred forty-eight patients were recruited for this ongoing clinical trial. Thus far, 83%-84% of participants in the intervention arms have completed the 1-year study.


DR. CROSS


DR. KANE

Elkjaer et al. evaluated the impact of a web-based treatment program and patient education center in a convenience sample of patients with UC.[10] All 21 patients reported the ability to initiate a self-care plan and experienced improvements in knowledge after interaction with the patient education center.[10] The web-based self-management and treatment approach was compared with standard of care in 333 patients with mild to moderate UC from Ireland and Denmark.[11] Only 135 patients (41%) completed the 1-year study. Web subjects were more adherent with acute treatment, demonstrated improved disease knowledge and quality of life, experienced shorter relapses, and had fewer office and urgent care visits.

A 2012 study by the same group investigated the efficacy of web-based monitoring of Crohn's disease activity for individualized dosing of infliximab maintenance therapy. Twenty-seven patients were enrolled; 17 completed 52 weeks and 6 completed 26 weeks of follow-up. Patients recorded their symptoms weekly via a web-based portal; on the basis of symptom scores, patients were instructed to contact their physician for an infliximab infusion. Fifty percent of the patients were able to tolerate intervals greater than 8 weeks, whereas 36% required shorter intervals.[12] This concept of web-based personalized treatment was further investigated in a 2014 study evaluating 86 patients with mild to moderate UC. Mesalamine treatment was individualized on the basis of a composite index of clinical symptoms and fecal calprotectin levels. Use of the web application was associated with decreased disease activity scores and lower fecal calprotectin levels despite dose reduction in 88% of patients at week 12.[13]

The eIBD program developed at the University of California, Los Angeles, also uses a web-based platform to monitor patients. After an initial training session with an IBD nurse specialist, patients are able to view clinical results and view and update their disease activity status, quality of life, and work productivity remotely. Patients interact with the eIBD program by using a tablet or home computer. Self-monitoring was found to correlate well with an in-person assessment of symptoms and disease activity.[14] Patient care is organized into evidence-based pathways on the basis of disease status and the medication regimen. When University of California, Los Angeles, IBD patients were compared with matched controls by using an administrative claims database, they were significantly less likely to use steroids and had fewer hospitalizations and emergency department visits.[15]

HealthPROMISE is an application developed at Mount Sinai to manage patient-reported symptoms and quality of life, which are integrated into the electronic medical records system; providers can view the information in real time to better manage their panel of patients. HealthPROMISE is currently being evaluated as part of a pragmatic, multicenter, randomized controlled trial.[16]

EncephalApp is a mobile phone application used to assess patients for hepatic encephalopathy. The application was shown to have excellent discriminant ability to detect encephalopathy, and importantly,

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EncephalApp times correlated with motor vehicle accidents and illegal turns in a driving simulation test.[17] A number of other mobile applications have been developed to support patients with chronic illnesses. These applications can be integrated with wearable devices, and some have been approved by the Food and Drug Administration.[18]

Telehealth and teleconsultation

Advancements in telemedicine have outpaced the ability of legislators and institutional officials to provide oversight on legal and regulatory issues. Each state sets requirements for providers to engage in telehealth activities. The ATA published the State Telemedicine Gap Analysis to address specific requirements and limitations for each state.[19] To promote telemedicine, the Federation of State Medical Boards proposed the development of an Interstate Licensure Compact in which 17 states participate.[20] Two key principles include defining the practice of medicine as the location in which the patient resides and placing the provider under the jurisdiction of the state in which the practice occurs. The TELE-MED Act of 2015 has proposed allowing Medicare physicians to provide telehealth services to patients regardless of the state in which they reside.[21] So far, the number of malpractice cases involving telemedicine services is low; most are related to e-prescribing, as opposed to care provided during teleconsultation services.[22]

However, some unique liability issues relative to telehealth encounters exist. First, when considering standard of care, what do you compare a telemedicine encounter with? Hardware or software malfunctions can occur, with a subsequent inability to provide the telemedicine service. Loss of protected health information through hackers or equipment failure is another potential threat. Reimbursement for telehealth services is also regulated by states and is subject to wide variability; 29 states have laws in place requiring private payers to reimburse for telehealth services at the same level as an in-person encounter.[19] The ATA recently published an analysis of issues related to reimbursements.[23]

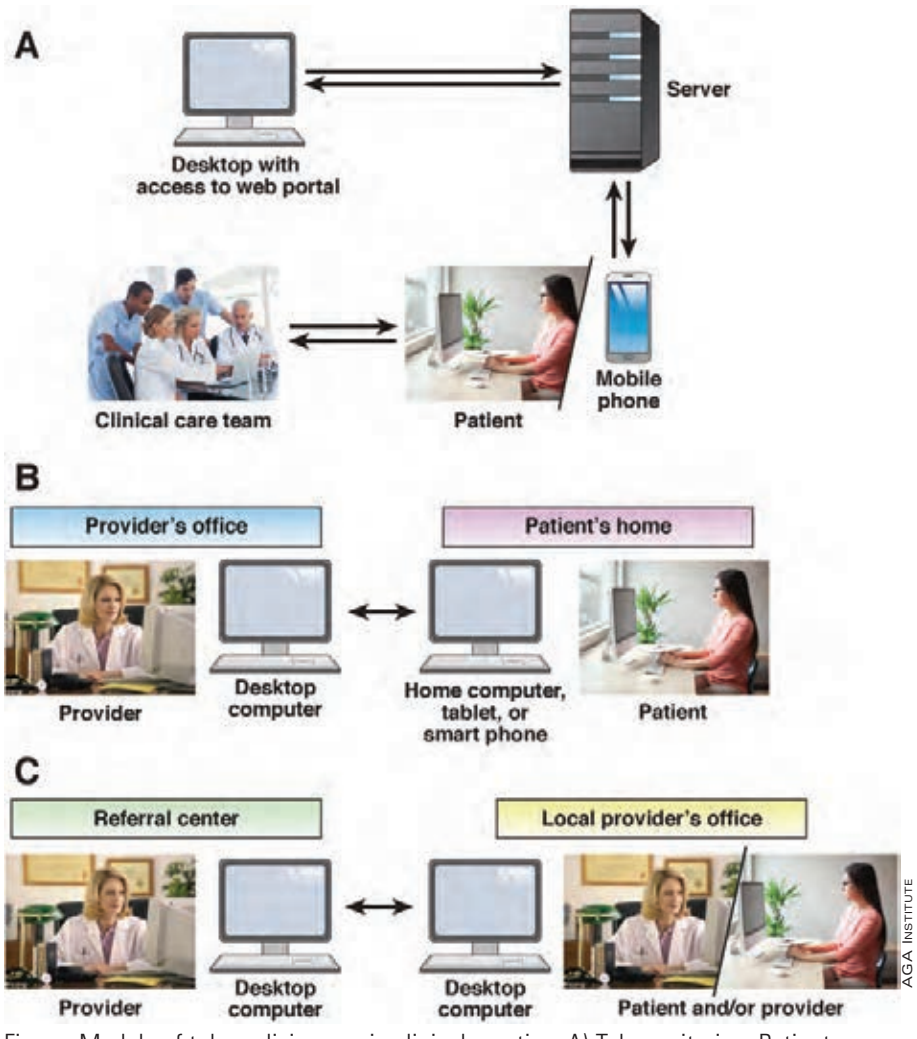

Figure. Models of telemedicine use in clinical practice. A) Telemonitoring. Patient interacts with health care team through use of some form of remote technology (cellular telephone, mobile application, or computer). After completing assessment, a medical team provides automated feedback and/or response to patients. B) Telehealth visits. Patient enters a "virtual exam room" at which time the patient and provider undergo a clinical encounter. C) Teleconsultation. This model is similar to (B). However, patient undergoes the telehealth visit in another provider's office. This model also allows for an interaction between the on-site provider and the remote provider with or without direct patient involvement.

Take-away points:

1. Telemedicine is the exchange of medical information from one to site to another to improve a patient's clinical health status; this includes two-way video, email, secure messaging, cellular phones (smartphones), and wireless tools.
2. The use of telemedicine has expanded in patients with digestive diseases because of the near universal patient access to a computer or cellular phone, suboptimal clinical outcomes, and patients' desire for a more efficient method to receive health care.
3. Patients with digestive diseases are accepting of telemedicine technology; use of telemedicine systems has been shown to improve disease knowledge, medication adherence, and quality of life and to decrease utilization of health care resources in some but not all studies.
4. Telehealth visits may improve access to gastroenterology specialty care and improve efficiency; however, barriers still exist for more widespread use including the requirement for a face-to-face visit and informed consent before a telehealth visit, reimbursement issues, and licensing requirements to provide services across state lines.

The Mayo Clinic, Rochester, Minn., offers outreach to its health system affiliates via a secure video conferencing platform to allow face-to-face consultations for patients with IBD. Consultative appointments are scheduled during preassigned blocks of outreach time on the clinician's calendar. Health care providers offering video consultation are required to have a medical license for the state in which the patient resides and to be credentialed by the facility to which the Mayo Clinic provides services and the payer reimbursing for the service. Access to imaging and laboratory work is facilitated through previsit evaluation performed by a nurse in the referring practice.

If services are provided via consultation to a patient at a non–Mayo Clinic facility via the Affiliated Care Network, there is a legal contract outlining reimbursement as well as terms and conditions. For asynchronous consultation where there is interaction with a provider but the patient is not directly involved (no face-to-face consultation), the practice of medicine regulations vary from state to state as outlined above. However, for all states, electronic health record documentation of the clinical question and recommendations is important. This is supported by a secure online portal that exchanges electronic health record information and the clinical note generated. The telehealth efforts at the Mayo Clinic are not isolated to gastroenterology; it is estimated that, through expanded use of telehealth, Mayo Clinic will provide care nationally and internationally for 200 million people by 2020.[24]

From April 2015 to May 2016, at the University of Maryland, Baltimore, we conducted 89 telehealth visits. According to state regulations and payer restrictions on reimbursement, patients were eligible to undergo telehealth visits if they had a prior face-to-face visit and were insured by Blue Cross Blue Shield. Eligible patients provided informed consent to participate in the telehealth visit. Patients received an email with instructions on how to download the required software (VidyoDesktop version 3.0.4[001]; Vidyo, Hackensack, N.J.) onto the patient's home computer, tablet, or smartphone. Seventy-one percent reported that the telehealth visit took significantly less or less time than a routine encounter; 88% said that all their concerns were addressed during the telehealth visit. All patients felt that telehealth visits were more convenient than a face-to-face encounter; 53% and 41% reported that the telehealth visit saved them 1-3 hours and more than 3 hours, respectively.

Teleconferencing

Project Extension for Community Health Care Outcomes (ECHO) was originally designed to provide specialist support for treatment of hepatitis C to primary care providers (PCPs) in rural New Mexico and the prison health system. The ECHO model leverages video teleconferencing to provide ongoing assistance from specialists to PCPs for management of cases, treatment plans, and monitoring and also provides case-based learning to increase PCP knowledge and opportunities to participate in

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research.[25] A survey of 29 providers participating in Project ECHO revealed that more than 90% of respondents felt comfortable with management of hepatitis C as a consequence of using the program.[26] Subsequently, a prospective cohort study was conducted to compare outcomes of treatment of hepatitis C between the University of New Mexico hepatitis C virus clinic and PCPs at 21 ECHO sites. In the 407 patients who were included in the cohort study, sustained virologic response was obtained in 57.5% and 58.2% of patients treated at University of New Mexico and ECHO sites, respectively. Adverse events were lower at ECHO sites, compared with the hepatitis C virus clinic (6.9% vs. 13.7%, respectively).[27] Similar approaches have been proposed to create multidisciplinary teams for the management of hepatocellular carcinoma and cirrhosis.[28]

The Inflammatory Bowel Disease Live Interinstitutional and Interdisciplinary Videoconference Education (IBD LIVE) is a national weekly teleconference that brings together gastroenterologists, surgeons, radiologists, pathologists, and medical subspecialists from multiple institutions to discuss the management of complex IBD cases. IBD LIVE is continuing medical education–accredited and is published quarterly in Inflammatory Bowel Diseases. Each 1-hour conference covers two cases equally. After the initial presentation, the moderator summarizes the case and asks faculty to provide their opinion on management. Because many of the cases presented are quite complex, it is common for subspecialists from other disciplines to join the conference to provide clarity.[29] Providers also use the summary and recommendations to help inform decisions in management of their respective patients.

Conclusions

The use of telemedicine in the care of patients with digestive diseases is expanding beyond telephone triage to include remote monitoring and self-care, telehealth visits, and teleconferencing. It is inevitable that use of these services will continue to increase to improve clinical care, to provide quality metrics, to increase access to gastroenterology care and tertiary referral expertise, to improve efficiency of health care delivery, and to decrease costs. Investment in telehealth by venture capitalists has increased fourfold from $1.1 to $4.3 billion from 2011 to 2015.[30] Unfortunately, barriers to providing health care remotely continue. These include technological barriers for many practices, the requirement for providers to be licensed and credentialed in multiple states and institutions respectively, unique liability concerns, difficulties with reimbursement, and differential access to telehealth services among patients. In addition, patient engagement with remote monitoring has been disappointing, likely because of poor system designs. It is likely that payers and states will slowly increase reimbursement and ease use of telemedicine as they learn how telemedicine can decrease costs and improve the efficiency of health care delivery.

Content from this column was originally published in the "Practice Management: The Road Ahead" section of Clinical Gastroenterology and Hepatology (2017;15:175-81).

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