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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

KELSEY GRIFFIN

Dr. John M. Inadomi, AGAF, of the University of Washington provides a perspective on the recommendation to start screening younger.

ACS: Start colorectal cancer screening at 45

BY ANDREW D. BOWSER
MDedge News

The American Cancer Society recommends all U.S. adults at average risk of colorectal cancer (CRC) undergo screening starting at age 45 years.

That update to ACS recommendations is based on an increasing burden of CRC in younger individuals, microsimulation modeling results, and a "reasonable expectation" that screening tests will perform as well in adults aged 45-49 years as they do in older adults, members of the ACS Guideline Development Group said in the guideline, which was published in CA: A Cancer Journal for Clinicians.

Starting screening at age 45 contrasts with recommendations from the U.S. Preventive Services Task Force (USPSTF), which in 2016 gave an "A" recommendation for CRC screening from 50 to 75 years of age. At the time, the USPSTF noted a modest increase in life-years gained by starting earlier, based on microsimulation modeling. But it concluded that available evidence best supported starting at age 50.

The updated ACS guidelines are based in part on a modeling study that the authors say extends the previous analysis conducted for the USPSTF.

"The recommendation places a high value on the

See **Screening** · *page 28*

Promising therapies for NAFLD, NASH now in phase 3 trials

BY IAN LACY
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Several treatments for nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) in phase 3 trials show promise for these complex disorders.

"When we talk emerging treatments in NASH, focusing on phase 3s [trials], there are really four drugs," Stephen Harrison, MD, medical director of Pinnacle Clinical Research, said at the annual Digestive Disease Week®. "There's elafibranor, obeticholic acid (OCA), selonsertib, and cenicriviroc. Each of these have their own phase 3."

The trials have different primary endpoints, an important factor, according to Dr. Harrison.

OCA, a promising drug for NASH, is approved by the Food and Drug Administration to treat primary biliary cholangitis. In FLINT (The Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment Trial), a double-blind, randomized, controlled phase 2 study, 141 patients received 25 mg of OCA daily for 72 weeks; 142 received placebo. By the study's end, 45% of 110 patients in the OCA group had improved

See **Trials** · *page 30*

Tenapanor shows safety, efficacy for irritable bowel syndrome

BY MITCHEL L. ZOLER
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Tenapanor, a first-in-class agent showed efficacy and safety for treating patients with constipation-predominant irritable bowel syndrome in a phase 3 multicenter, U.S. trial with 593 patients.

These data combined with results from an already reported additional phase 3 trial and a phase 2 study will go to the Food and Drug Administration later in 2018 in an application for marketing approval for tenapanor, according to William D. Chey, MD, AGAF, who spoke at the annual

See **Tenapanor** · *page 19*

News from DDW2018 Digestive Disease Week® in this issue

INSIDE

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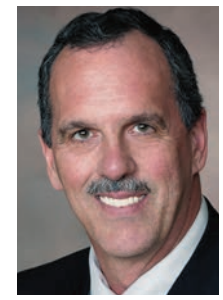
LETTER FROM THE EDITOR: Consolidation of health care dollars


DR. ALLEN

Research shows the ocean's cod population is diminishing to dangerously low levels. In response, several countries (the United States, Iceland, and others) have instituted a resource allocation system termed "catch share," where each fisherman is allotted an annual number of fish. Shares can be leased, bought, and traded. Consequently, there has been horizontal and vertical consolidation within the industry and huge fishing corporations have emerged while independent small-boat fishermen have virtually disappeared. Once consolidation occurred, venture capital entered the market. Parallels to what is happening to independent medical practices should not be ignored.

We have closed the book on DDW® 2018. Researchers presented new and innovative studies that will directly affect our practices. I was honored to give the "Best of AGA – DDW" lecture where I chose only seven of hundreds of abstracts to present. All DDW lectures are located at https://watch.ondemand.org/ddw. *GI & Hepatology News* will highlight several high-impact presentations is this and subsequent issues.

This month, our cover stories include a new ACS recommendation to drop the age of first colon cancer screening to 45 (see perspective by John M. Inadomi, MD, AGAF). Two of our most intractable disorders (NAFLD and IBS) have new therapies in the pipeline. From the AGA journals we have articles on Barrett's surveillance, diet, cognitive-behavioral therapy for IBS, and better monitoring methods for Crohn's disease.

July begins a new fiscal year for many of us. For many health systems, this last year saw diminishing clinical margins, increased regulations, dramatic alterations in pharmaceutical funds flow, and price pressures that are increasing. I sit on the board of a large nonprofit (nonacademic) Minnesota health system, and I am a member of key financial committees within Michigan Medicine. The learnings and contrasts from each are immense. Health care delivery in both systems is based on high fixed costs and margins that require cost reductions in the 3%-5% range per year to remain viable. Implications for physicians in all settings are immense. That said, there are solutions as you will see in coming publications.

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

DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz

Q1. A 60-year-old woman is admitted to the hospital with an upper GI bleed and found to have a gastric ulcer. Biopsies from the ulcer show no malignancy. Gastric biopsies reveal no *Helicobacter pylori*, and stool antigen for *H. pylori* is also negative. The patient denies any NSAID use. She is discharged home on twice-daily PPI. Two months later, she returns for a follow-up endoscopy, and the ulcer has healed.

What is your recommendation for this patient?
A. Continue once-daily PPI indefinitely
B. Discontinue PPI
C. Continue once-daily PPI for 2 more months
D. Discontinue PPI and start sucralfate

Q2. A 54-year-old woman presents for management of moderately severe ileocolonic Crohn's disease. She has a strong family history of multiple sclerosis and recently noted some tingling in her toes for which she is undergoing neurologic evaluation. She has had two small basal cell carcinomas removed from her cheek in the last year. She received the BCG vaccine as a child and had a positive PPD skin test within the last year. Laboratory evaluation reveals HBsAg negative, anti-HBs positive, and anti-HBc positive; JC virus antibody is positive.

Which of the following is the strongest reason to avoid anti–tumor necrosis factor therapy in this patient?
A. Current neurologic symptoms
B. History of skin cancer
C. Positive PPD skin test
D. Infection with hepatitis B
E. Presence of JC virus antibody

The answers are on page 18.

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FROM THE AGA JOURNALS

Diverse factors predicted Barrett's progression

BY AMY KARON
MDedge News

Older age, male sex, smoking, longer segment length, and low-grade dysplasia were significant risk factors for progression of Barrett's esophagus (BE) in a meta-analysis of 20 studies.

"Individuals with these features should undergo more intensive surveillance or endoscopic therapy," Rajesh Krishnamoorthi, MD, of Mayo Clinic in Rochester, Minn., and his associates wrote in the July issue of Clinical Gastroenterology and Hepatology. "Smoking is a modifiable risk factor for cancer prevention in patients with BE."

"Currently, gastrointestinal societies' guidelines on BE surveillance are solely based on dysplasia grade and do not take into account any of the other risk factors," the reviewers concluded. Their findings could form the backbone of a risk score that identifies high-risk BE patients with baseline low-grade dysplasia or nondysplastic BE "who would benefit from intensive surveillance or endoscopic therapy."

Esophageal adenocarcinoma is on the rise and fewer than one in five patients survive 5 years past diagnosis. Endoscopic surveillance for esophageal adenocarcinoma is recommended in Barrett's esophagus, but only about 1 in 10 esophageal adenocarcinoma patients has a preceding BE diagnosis. "This ostensible discrepancy has raised concerns about the effectiveness of current screening and surveillance programs," the reviewers noted. Studies also have yielded conflicting evidence about the value of endoscopic surveillance as currently performed.

To help prioritize BE patients for surveillance, the reviewers searched EMBASE, MEDLINE, and Web of Science from inception through May 2016 for cohort studies of risk factors for progression of BE among patients with either no dysplasia or low-grade dysplasia.

The 20 studies covered 1,231 BE progression events among 74,943 patients. In separate pooled estimates, progression of BE correlated significantly with older age (odds ratio, 1.03; 95% confidence interval, 1.01-1.05), male sex (OR, 2.2; 95% CI, 1.8-2.5), current or former smoking (OR, 1.5; 95% CI, 1.09-2.0), and greater BE segment length (OR, 1.3; 95% CI, 1.16-1.36). Results tended to be homogeneous among studies, said the reviewers. Low-grade dysplasia correlated strongly with progression (OR, 4.3; 95% CI, 2.6-7.0), while use of proton pump inhibitors (OR, 0.55; 95% CI, 0.32–0.96) and statins (OR, 0.48; 95% CI, 0.31-0.73) showed the opposite trend. "Alcohol use and obesity did not associate with risk of progression," the reviewers added.

Thirteen studies in the meta-analysis were from Europe, six were from the United States, and one was from Australia. Ten were multicenter studies, 13 were deemed high quality, 3 were deemed medium quality, and 4 were deemed low quality. The reviewers were unable to assess dose-response relationships for relevant factors, such as alcohol, tobacco, and medications, and not all studies accounted for potential confounding.

Only four studies included multivariate analyses to control for the confounding effects of age, sex, and BE characteristics (length and dysplasia). When the reviewers analyzed only these studies, older age and smoking no longer predicted BE progression. Use of proton pump inhibitors remained protective, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) became protective, while statin use lost significance.

The reviewers disclosed no external funding sources or conflicts of interest.

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SOURCE: Krishnamoorthi R et al. Clin Gastroenterol Hepatol. 2017 Nov 30. doi: 10.1016/j.cgh.2017.11.044.

Endoscopic surveillance is currently recommended for nondysplastic Barrett's esophagus (BE), but there are conflicting results on the effectiveness of surveillance on esophageal adenocarcinoma outcomes. This meta-analysis by Krishnamoorthi et al. found several risk factors associated with BE progression (i.e., age, male sex, smoking, BE length) among patients with nondysplastic BE or low-grade dysplasia. Current recommendations for BE surveillance intervals are based solely on dysplasia grade without consideration for other high-risk features (i.e., smoking, BE length, age). This meta-analysis demonstrates that some patients with nondysplastic BE are at a higher risk of neoplastic progression, and the AGA recommendation for BE surveillance every 3-5 years may not be suitable for all.

DR. TAN

In addition, proton pump inhibitor, statin, and nonsteroidal anti-inflammatory drug use were associated with lower risk of BE progression, although inconsistently in studies that adjusted for age, sex, and BE characteristics. Current studies on medication chemoprevention of neoplastic progression in BE are limited by residual confounding inherent in observational studies. I anticipate that the results of the Oxford AspECT clinical trial on chemoprevention with esomeprazole with or without aspirin will conclusively answer this question.

Parasa et al. recently developed a risk prediction model to stratify risk of progression in patients with nondysplastic BE based on BE length, male sex, smoking, and baseline low-grade dysplasia. Patients with one or more of these risk factors are at highest risk of neoplastic progression and may benefit from shorter surveillance intervals or endoscopic eradication therapy.

Mimi C. Tan, MD, MPH, is a postdoctoral fellow in gastroenterology and hepatology, T32 research track at Baylor College of Medicine, Houston, and an investigator at the Center for Innovations in Quality, Effectiveness, and Safety at the Michael E. DeBakey VA Medical Center, Houston. She has no conflicts.

Mediterranean diet cut fatty liver risk

BY AMY KARON
MDedge News

Middle-aged and older adults who closely followed a Mediterranean-style diet for 6 years were at significantly lower risk of developing fatty liver disease than others in a large prospective study reported in the July issue of Gastroenterology.

Each 1–standard deviation rise in Mediterranean-style Diet Score (MDS) correlated with significantly decreased hepatic fat accumulation and a 26% lower odds of new-onset fatty liver disease ($P = .002$). "To our knowledge, ours is the first prospective study to examine the relations of long-term habitual diet to fatty liver," Jiantao Ma, MBBS, PhD, and his associates wrote. "Our findings indicate that improved diet quality may be particularly important for those with high genetic risk for NAFLD."

The Mediterranean diet emphasizes fruits, vegetables, nuts, legumes, whole grains, and omega-3 fatty acids and minimizes consumption of *trans* fats and red meat. The diet has been linked with reduced liver fat in a large cross-sectional study and a 6-week randomized trial of patients with nonalcoholic fatty liver disease (NAFLD). In the current study, 1,521 middle-aged and older adults from the Framingham Heart Study self-administered the 126-item Harvard food-frequency questionnaire during 2002 through 2005 and 2008 through 2011. Longitudinal changes in two diet scores, the MDS and the Alternative Healthy Eating Index (AHEI), were correlated with hepatic fat based on liver phantom ratio and computed tomography.

Over a median 6 years of follow-up, each 1–standard deviation rise in MDS correlated with a 26% decrease in odds of new-onset fatty liver (95% confidence interval, 10%-39%; $P = .002$) and with a significant increase in liver phantom ratio (0.57; 95% CI, 0.27-0.86; P less than .001), which signifies lower accumulation of liver fat. Similarly, every 1–

Continued on following page

FROM THE AGA JOURNALS

Home-based CBT significantly improved IBS symptoms

BY AMY KARON
MDedge News

Primarily home-based cognitive-behavioral therapy (CBT) improved irritable bowel syndrome (IBS) symptoms at least as much as conventional CBT, cut clinician time by 60%, and significantly outperformed educational sessions in a multicenter clinical trial reported in the July issue of Gastroenterology.

Acutely, primarily home-based CBT produced a mean 61% improvement in self-reported symptoms on the IBS version of the Clinical Global Impressions Scale, versus 44% for the educational control group (*P* less than .05), wrote Jeffrey M. Lackner, PsyD, of the State University of New York at Buffalo and his associates. Blinded gastroenterologists reported improvements of 56% and 40%, respectively (*P* less than .05). The superiority of the minimal-contact CBT program held up at 6 months and equivalence tests found it "at least as effective as standard CBT," the researchers wrote.

IBS is a major area of unmet clinical need that costs the United States some $28 billion annually. Clinicians and patients lack both reliable biomarkers and "uniformly effective" therapies, the investigators noted. In recent years, severe adverse events have greatly restricted the availability of otherwise promising Food and Drug Administration–approved therapies, such as Lotronex (alosetron hydrochlorine), which has been linked to ischemic colitis and fatal cases of ruptured bowel, and Zelnorm (tegaserod maleate), which has been associated with myocardial infarction, stroke, and unstable angina.

In contrast, face-to-face CBT is safe, efficacious, and guideline recommended for IBS. However, uptake is limited by cost, stigma, geography, and a shortage of certified providers, the researchers noted. They enrolled 436 patients with IBS based on Rome III criteria and randomly assigned them to one of three interventions. The standard CBT group received 10 weekly, 60-minute, face-to-face CBT sessions on brain-gut interactions, symptom triggers and monitoring, muscle relaxation, worry control, problem solving, and relapse prevention. The primarily home-based CBT group covered the same topics but attended only four clinic sessions and was provided home study materials. Finally, the education group attended four sessions with background information on IBS and the role of stress, diet, and exercise.

Baseline characteristics were comparable among groups, as were dropout rates (9% overall). In all, 89% of patients completed at least 8 of 10 standard CBT sessions or at least three of four home-based CBT or educational sessions. Six months after the interventions ended, primarily home-based CBT continued to outperform education (blinded gastroenterologist-reported improvements, 58.4% and 44.8%, respectively; *P* = .05 for difference between groups).

Equivalence tests indicated that the minimal-CBT intervention was at least as effective as standard CBT, and improvements were not primarily the result of concomitant medications, according to the researchers. Nonetheless, only 42% of patients who benefited from CBT achieved remission, defined as no or mild IBS symptoms on the gastroenterologist-administered Clinical Global Impressions Scale. Unremitted patients might benefit from combining CBT with medical therapies that target both "central and peripheral mechanisms of IBS," the investigators said.

The three interventions produced comparable acute and longer-term improvements on the IBS Symptom Severity Scale, which emphasizes sensory symptoms and therefore might be a less-sensitive endpoint than the Clinical Global Impressions Scale, the researchers noted. Nonetheless, CBT produced some of the strongest absolute symptomatic improvements ever reported for IBS.

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

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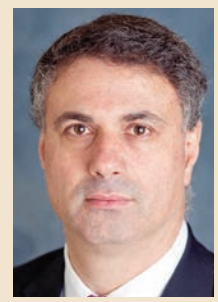
SOURCE: Lackner JM et al. Gastroenterology. 2018 Apr 24. doi: 10.1053/j.gastro.2018.03.063.

Treating the myriad symptoms of IBS patients remains a great challenge in clinical practice. A bigger challenge is the management of IBS patients who are refractory to medical therapy, which commonly includes a combination of pain, bowel, and psychiatric medications. In this very well-designed and -executed study, Lackner and his colleagues randomized such IBS patients with moderate to severe symptoms to three therapeutic arms: standard CBT, minimal-contact home-based CBT, and IBS education. The authors demonstrated that 4-session home-based CBT was as efficacious as 10 sessions of standard CBT and both were significantly more efficacious than IBS education in global improvement of IBS symptoms. The superior effect of both types of CBT was maintained over a period of 6 months post treatment.


DR. FASS

There are several important conclusions from this pivotal trial. First, the study further cemented the therapeutic value of CBT in the management of IBS patients, especially for those patients who are refractory to the currently available medical therapy. Because of the size of the study and the rigorous design, it is probably the best evidence we currently have about the value of CBT in IBS. Second, minimal-contact home-based CBT is as effective as standard CBT in controlling the full range of IBS symptoms. The former may be preferred by IBS patients, who are not available or may not be compliant with repeated clinic visits for standard CBT sessions. Standard CBT is typically lengthy and expensive. The minimal-contact home-based CBT option has the benefit of being more accessible and less costly, and most importantly, it does so in a way that does not compromise the therapeutic value of symptom relief.

The exact duration of symptom control that can be achieved post CBT and the value of other psychological interventions in IBS patients remain to be elucidated.

Ronnie Fass, MD, is a professor of medicine at Case Western Reserve University, Cleveland, as well as the medical director of the Digestive Health Center and director of the division of gastroenterology and hepatology, head, esophageal and swallowing center at MetroHealth Medical Center, also in Cleveland. He has no conflicts of interest.

Continued from previous page

standard deviation rise in the AHEI dietary score correlated with a 0.56 rise in liver phantom ratio (95% CI, 0.29-0.84; *P* less than .001) and with a 21% lower odds of incident fatty liver disease (95% CI, 5%-35%; *P* = .02).

Individuals whose diets improved the most (those in the highest quartile of dietary score change) over time had about 80% less liver fat accumulate between baseline and follow-up, compared with those whose diets worsened the most (those in the lowest quartile). Furthermore, relationship between diet and liver fat remained significant (*P* = .02) even after accounting for changes in body mass index.

The investigators also studied whether the presence of single nucleotide polymorphisms (SNPs) linked with NAFLD modified dietary effects. High genetic risk for NAFLD did not appear to lead to increased liver fat as long as diet improved or remained stable over time, they found. But when diet worsened over time, high genetic NAFLD risk did correlate with significantly greater accumulation of liver fat (*P* less than .001).

"Future intervention studies are needed to test the efficacy and efficiency of diet-based approaches for NAFLD prevention as well as to examine mechanisms underlying the association between diet and NAFLD," the researchers wrote.

The National Heart, Lung, and Blood Institute's Framingham Heart Study provided funding. Affymetrix provided genotyping. The researchers reported having no financial conflicts of interest.

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SOURCE: Ma J et al. Gastroenterology. 2018 Mar 28. doi: 10.1053/j.gastro.2018.03.038.

FROM THE AGA JOURNALS

Fecal calprotectin levels predicted mucosal, deep healing in pediatric Crohn's

BY AMY KARON
MDedge News

For children with Crohn's disease (CD), fecal calprotectin levels below 300 mcg indicated mucosal healing, while values below 100 mcg signified deep healing in a multicenter, 151-patient study.

Sensitivity was 80% for mucosal healing and 71% for deep healing, while specificities were 81% and 92%, respectively, said Inbar Nakar of the Hebrew University of Jerusalem, with her associates. In line with prior studies, adding C-reactive protein (CRP) to fecal calprotectin improved neither sensitivity or specificity, the researchers wrote in the July issue of Clinical Gastroenterology and Hepatology.

Bowel healing is a crucial goal in CD. Because pediatric transmural healing had not been studied, the researchers analyzed data from the ImageKids study, a multicenter effort to develop magnetic resonance enterography (MRE) measures for CD patients aged 6-18 years. Participants averaged 14 years old with a standard deviation of 2 years. Assessments included MRE, complete ileocolonoscopic evaluation, CRP, and fecal calprotectin. The researchers defined mucosal healing as a Simple Endoscopic Severity Index in Crohn's Disease score below 3, transmural healing as an MRE visual analog score below 20 mm, and deep healing as transmural plus mucosal healing.

"Although a calprotectin cutoff [less than] 300 mcg/g predicted mucosal healing, a lower cutoff of [less than] 100 mcg/g may be more suitable to predict deep healing."

Nearly one-third of patients had healing only in the mucosa or the bowel wall, but not both; 6% had mucosal healing but transmural inflammation, and 25% of children had transmural healing but mucosal inflammation. In addition, 14% of children had deep healing, and 55% of children had both mucosal and transmural inflammation. Those findings highlight "the discrepancy between mucosal and transmural inflammation and the importance of evaluating the disease by both ileocolonoscopy and imaging," the researchers wrote.

Median calprotectin levels varied significantly by healing status (*P* less than .001). They were lowest (10 mcg/g) for deep healing, followed by either transmural or mucosal inflammation, and were highest (median, 810 mcg/g) when children had both mucosal and transmural inflammation.

Calprotectin in children with deep healing had an area under the receiver operating characteristic curve value of 0.93 (95% confidence interval, 0.89-0.98). In contrast, CRP level identified children with deep healing with an AUROC value of only 0.81 (95% CI, 0.71-0.90).

Although "calprotectin level is driven primarily by mucosal healing, [it] is still superior to CRP," the investigators concluded. "Although a calprotectin cutoff [less than] 300 mcg/g predicted mucosal healing, a lower cutoff of [less than] 100 mcg/g may be more suitable to predict deep healing." However, they emphasized that fecal calprotectin level is only moderately accurate in predicting mucosal or transmural healing in children with CD. They advised physicians to "be familiar with the predictive values of each cutoff before incorporating them in clinical decision making."

An educational grant from AbbVie funded the ImageKids study. AbbVie was not otherwise involved in the study. Two coinvestigators disclosed ties to AbbVie and other pharmaceutical companies. There were no other disclosures.

ginews@gastro.org

SOURCE: Nakar I et al. Clin Gastroenterol Hepatol. 2018 Mar 2. doi: 10.1016/j.cgh.2018.01.024.

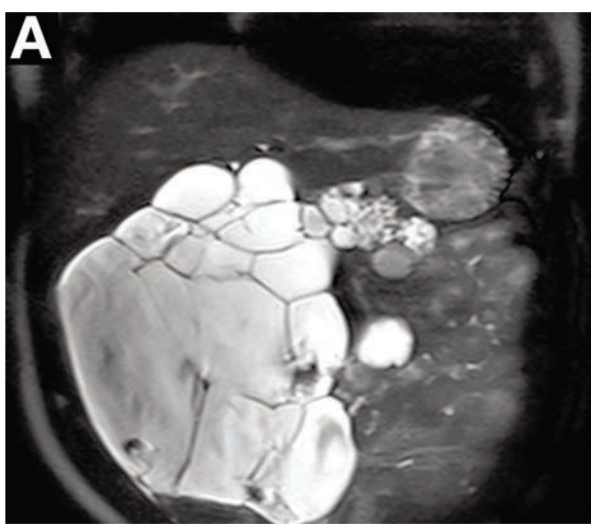
CLINICAL CHALLENGES AND IMAGES

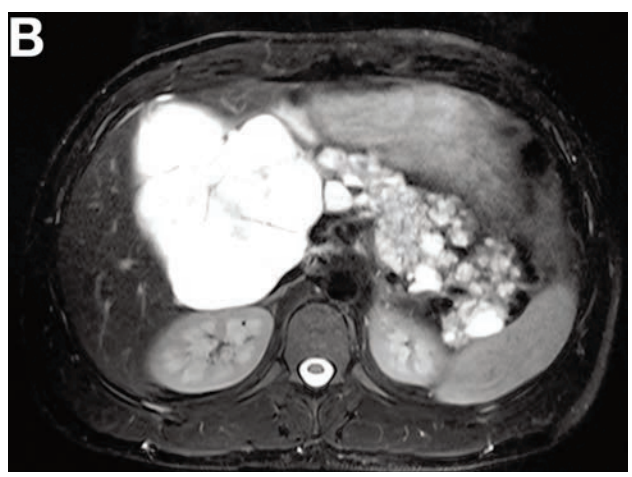
What is your diagnosis?

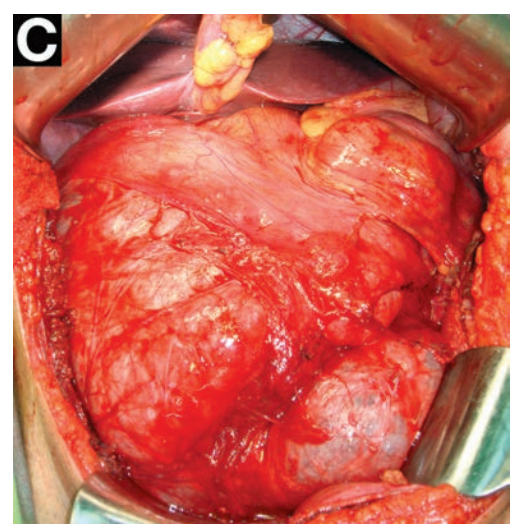
By Georgios C. Sotiropoulos, MD, PhD, Stylianos Karatapanis, MD, and Gregory Kouraklis, MD. Published previously in Gastroenterology (2016;151[5]:813-4).

A 25-year-old male patient was admitted for weight loss and increasing abdominal discomfort. On physical examination, a large mass was palpated in the upper abdomen. Laboratory tests were all within normal range. Abdominal ultrasound and cross-sectional imaging (computed tomography, magnetic resonance imaging) revealed an enormous cystic tumor in right abdomen, 25 × 20 cm in size; the tumor occupied almost half of the abdominal cavity (Figures A, B). Concomitant kidney or liver cysts were absent. At operation, a giant polycystic tumor producing considerable compression of neighbor organs was evident (Figure C). The tumor was completely removed. What is your diagnosis?

The diagnosis is on page 26.







AGA opens GI Patient Center to the public

We're proud to announce the public launch of the AGA GI Patient Center, an online hub for digestive health information developed by specialists, for patients. The GI Patient Center – previously accessible only by AGA member physicians – now directly provides patients with trusted information on a variety of GI conditions and procedures.

Browse the GI Patient Center, which includes information on more than 30 topics, available in both English and Spanish. All AGA patient education was written and reviewed by leading gastroenterologists, and developed with health literacy in mind.

You can print this information for your practice, email patients a link, include a link on your website – whatever is needed to ensure your patients are getting trusted health information about their condition, treatment, or procedure. To get started, visit patient.gastro.org.

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AGA announces its newest Fellows

AGA Fellowship status is an honor awarded to members who demonstrate a personal commitment to the field of gastroenterology and professional achievement in clinical private or academic practice and in basic or clinical research.

The most recent inductees into the AGA Fellows Program were recognized at Digestive Disease Week® (DDW) 2018 and received a digital ribbon in their AGA Community profile. The 2018 class of AGA Fellows includes 112 members, who added the designation "AGAF."

Join the AGA Fellowship Recognition Panel in congratulating these distinguished members and also view the 2018 class of AGA Fellows in the AGA Community forum, community.gastro.org.

Applications for the 2019 cohort are now being accepted. Those who meet the AGAF criteria are invited to apply. Applications are due Aug. 27, 2018. Learn more at gastro.org/fellowship.

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How does the Quality Payment Program affect you?

AGA asks Congress and the Centers for Medicare & Medicaid Services to continue to implement the Quality Payment Program (QPP) in a way that maximizes flexibility and success for you and your Medicare patients.

Most gastroenterologists participate in the Merit-Based Incentive Payment System (MIPS), which means how the QPP is implemented impacts the entire GI profession. The QPP replaced the SGR formula in 2015 when MACRA was signed into law. The QPP is composed of two tracks: MIPS and Advanced Alternative Payment Models (Advanced APMs).

CMS has designated 2017 and 2018 as transition years to allow providers to learn about the QPP and to gradually increase their preparedness for MIPS.

Congress also recently acted to provide CMS additional flexibility with respect to QPP and MIPS implementation, including:

- Excluding Medicare Part B drug costs from MIPS payment adjustments.
- Eliminating improvement scoring for the cost performance category for the second through fifth years of MIPS.
- Allowing CMS to weight the cost performance category at less than 30%, but not less than 10% for the years 2 through 5 of MIPS.
- Allowing CMS flexibility in setting the performance threshold for MIPS in years 2 through 5 to ensure a gradual and incremental transition to the performance threshold set at the mean or median for year 6.

QPP implementation is a top priority for AGA to ensure that the value of specialty care is recognized. Learn more on our website www.gastro.org/QPP.

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Introducing the 2018 class of AGA Research Foundation awardees

The American Gastroenterological Association (AGA) and the AGA Research Foundation are pleased to award 41 investigators with more than $2 million in research funding in the 2018 award year.

"We were impressed by the quality of applications received in 2018," said Robert S. Sandler, MD, MPH, AGAF, chair of the AGA Research Foundation. "The AGA Research Foundation is excited to add 41 investigators into the AGA Research Foundation awards family, and we look forward to seeing the results of their research. Based on the proposals, we are confident that the newest class of awardees will continue to push gastroenterology and hepatology research forward and contribute to the next big discoveries in our field."

The AGA Research Foundation Awards Program works to recruit, retain, and support the most promising investigators in gastroenterology and hepatology. With AGA Research Foundation funding, recipients have protected time to continue their fundamental research into causes and treatments for various digestive disorders. AGA grants have launched the careers of investigators doing important work that has translated to new patient care tools for clinicians, as well as better outcomes for patients. To view the full list of recipients, go to https://www.gastro.org/press-release/introducing-the-2018-class-of-aga-research-foundation-awardees.

The awards program is made possible thanks to generous donors and funders contributing to the AGA Research Foundation. Learn more about the AGA Research Foundation at www.gastro.org/foundation.

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Genes, not adiposity, may be driving appetite

BY KARI OAKES
MDedge News

BOSTON – Evidence from a twin study points to genes, rather than just adiposity, as the underlying factor in differences in appetite and satiety that have been observed in obesity.

The work adds a new dimension – and some questions – to previous research, which suggested individuals with obesity show heightened brain activation to food cues, especially calorically dense food.

"We thought it was fat mass ... but when we controlled for everything that monozygotic pairs have in common, that relationship went away, implicating something that the monozygotic twins have in common; i.e., genetics," said Jennifer Rosenbaum, MD, in a video interview at the annual meeting of the American Academy of Clinical Endocrinologists.

Dr. Rosenbaum, a fellow at the University of Washington, Seattle, and her collaborators made use of a statewide twin registry to conduct an extensive investigation of subjective and objective measures of appetite and satiety in the 42 twin pairs.

Twins had a mean age of 31 years; 27 of the twin pairs were monozygotic, Dr. Rosenbaum said. At least one member of each twin pair met criteria for obesity, and participants had a mean body mass index of 32.8 kg/m^2.

On the study day, participants arrived in fasting state and had a fixed-calorie breakfast equivalent to 10% of their daily caloric needs.

Then, participants received the first of two functional MRI scans; during the scan, they were shown images of high-calorie foods, low-calorie foods, and nonfood objects, and completed ratings of how appealing they found each image. After consuming another standardized meal equivalent to 20% of daily caloric needs, patients repeated the fMRI scan was repeated.

Finally, participants were given access to a buffet meal.

"When compared with how much fat mass they had, there was no relationship between how hungry or full they were when they were fasting, how hungry or full they were with a snack, or when they ate the buffet. It just didn't matter how much fat mass they had" for subjective reporting of hunger and fullness.

However, there was a direct correlation between fat mass and amount consumed at the ad libitum buffet.

As fat mass went up, areas of the brain implicated in appetite showed more activity when tempting images of high-calorie foods were presented.

Next, the researchers compared the brain activation of the twin with the higher fat mass with that of the twin with lower fat mass. Instead of seeing the same correlation between higher adiposity and greater brain activation, "we lost that relationship between how many calories they would eat and how their brain activated with the food," said Dr. Rosenbaum.

The study was funded by the National Institutes of Health. Dr. Rosenbaum reported no financial disclosures.

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DDSEP eight
Digestive Diseases Self-Education Program

Answers

Q1. Correct Answer: A

Rationale

This patient has an idiopathic, non-NSAID, non–*H. pylori*–associated ulcer and should be on daily PPI indefinitely. These patients have a high rate of recurrent bleeding (42%) and mortality when followed prospectively without being on antisecretory therapy. Although no randomized trials have assessed the benefit of medical cotherapy in this population, antiulcer therapy seems to reduce recurrent idiopathic ulcers.

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Q2. Correct Answer: A

Rationale

Anti–tumor necrosis factor (anti-TNF) therapy is relatively safe and well tolerated. However, there are a few important issues to consider prior to initiation of therapy. There is a risk of reactivation of both *Mycobacterium tuberculosis* and hepatitis B. In this patient's case, her PPD positivity is likely a false positive from remote BCG vaccination. An interferon-gamma release assay (e.g., QuantiFERON®) can be checked to confirm this; even if that is positive, in the absence of active tuberculosis (TB), she can be treated for latent TB for several weeks prior to initiation of anti-TNF therapy. Her hepatitis B serologies do not suggest chronic infection but rather prior infection with resolution. In this case, anti-TNF therapy is not precluded; rather, the AGA recommends considering concurrent antiviral prophylaxis while on anti-TNF therapy. Anti-TNF agents are not known to significantly increase the risk of progressive multifocal leukoencephalopathy like the nonselective anti-integrin natalizumab, so JC virus antibody positivity does not preclude their use. There is a slight increased risk of melanoma in those on anti-TNF therapy; nonmelanoma skin cancers are of greater concern in those on thiopurine therapy. Finally, anti-TNF therapy should be avoided in those with demyelinating diseases or those at high risk for such diseases.

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Shingles hospitalization more common in IBD patients

BY MITCHEL L. ZOLER
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Hospitalizations for shingles is twice as common among patients with inflammatory bowel disease than in the general U.S. population, based on analysis of data from the National Inpatient Sample.

This elevated risk for patients with inflammatory bowel disease (IBD) to develop a herpes zoster virus (HZV) reactivation severe enough to put them in the hospital makes it especially important for IBD patients to receive immunization against shingles, especially now that a more effective vaccine is available, Daniela G. Vinsard, MD, said at the annual Digestive Disease Week.® Ideally, IBD patients should receive the full course of the adjuvanted, recombinant zoster vaccine Shingrix before starting an immunosuppressive regimen, said Dr. Vinsard, a physician at the University of Connecticut, Farmington.

This finding, which underscored the susceptibility of IBD patients to shingles because of their immunosuppressive treatments and the importance of vaccination, recently became even more relevant when the Food and Drug Administration approved tofacitinib (Xeljanz) to treat ulcerative colitis in late May, said Gil Y. Melmed, MD, AGAF, director of clinical inflammatory bowel disease at Cedars-Sinai Medical Center, Los Angeles. Tofacitinib, which may be an attractive option to some patients as an oral immunomodulator, carries a black-box warning about the added risk for certain serious infections while taking the drug, including HZV. Recent recommendations from the American College of Gastroenterology said that IBD patients aged 51 years or older should "strongly consider" HZV vaccination, including immunosuppressed patients (Am J Gastroenterol. 2017 Feb; 112[2]:241-58). The introduction of a potentially popular drug for ulcerative colitis that's known to pose a risk for shingles might lead to a stronger recommendation for vaccination in the near future, Dr. Melmed said in an interview.

Mitchel L. Zoler/MDedge News

The finding highlights the importance of immunization against shingles, said Dr. Daniela G. Vinsard.

The study Dr. Vinsard reported used data collected by the National Inpatient Sample from 2012 to September 2015, which represented, with weighting, more than 142 million hospitalized American patients. From this data set she and her associates identified 7,180 IBD patients hospitalized with a primary diagnosis of a vaccine-preventable disease, and about 589,000 weighted patients hospitalized for a vaccine-preventable disease but without IBD. The selection also focused on patients aged 18-65 years. Dr. Vinsard said that she excluded older patients to eliminate advanced age as a cause of immunosuppression.

Among the IBD patients, HZV was the most frequent primary diagnosis, causing 35% of these hospitalizations. Other common infectious causes of hospitalization in this group were hepatitis B virus in 31% of cases, influenza in 22%, pneumonia in 9%, and other types of infections in the remaining 3%. In contrast, hepatitis B caused 35% of hospitalizations in patients without IBD, influenza caused 29%, pneumonia caused 14%, HZV caused 19%, and other infections accounted for 3% of admissions.

In a multivariate analysis that controlled for diabetes, HIV infection, cancer, and transplantation, the IBD patients had more than twice the rate of hospitalization for shingles, compared with the patients without IBD, Dr. Vinsard said. When broken down by specific disease type, the rate of HZV infection was 110% higher among ulcerative colitis patients, compared with the general population, and was 140% higher in Crohn's disease patients, both statistically significant differences.

An additional finding from the analysis was that during the 4 years of study, the rate of hospitalizations of IBD patients for influenza steadily rose, from about 10% in 2012 to nearly 30% in 2015.

Dr. Vinsard reported no disclosures. Dr. Melmed reported consulting with Pfizer, the company that markets tofacitinib, and with several other companies that market biological agents.

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Novel treatment added

Tenapanor *from page 1*

Digestive Disease Week.®

"Tenapanor may represent a novel, effective treatment option" for patients with constipation-predominant irritable bowel syndrome (IBS-C), said Dr. Chey, a professor of medicine and director of the GI Physiology Laboratory at the University of Michigan in Ann Arbor.

The study results met the trial's primary endpoint, the percentage of patients with a combined response consisting of at least a 30% drop from baseline in reported abdominal pain and an increase of at least one complete spontaneous bowel movement (CSBM) per week for 6 of the first 12 weeks of treatment. This combined response occurred in 37% of patients treated with tenapanor at a dosage of 50 mg orally b.i.d., compared with a 24% rate among the placebo-control patients, a statistically significant difference, Dr. Chey reported.

The most common adverse effect seen in the tenapanor-treated patients was diarrhea, which occurred in 16% of the drug-treated patients and in 4% of controls. "I think diarrhea is an expected adverse effect," Dr. Chey said. Overall, treatment-related adverse effects occurred in 23% of tenapanor-treated patients and in 9% of controls, serious adverse effects occurred in 4% of patients on tenapanor and in 3% of controls, and adverse effects leading to treatment discontinuation occurred in 8% on tenapanor and in 1% of controls. Aside from diarrhea, the other most common adverse effects linked with tenapanor treatment were abdominal distension, in 3%, and flatulence, also in 3%.

Tenapanor is an inhibitor of sodium/hydrogen exchanger isoform 3, the predominant intestinal sodium transporter. Through this inhibition tenapanor reduces sodium uptake in the gut, causing increased intestinal fluid volume and shorter transit time and thereby softening stool consistency and increasing bowel movement frequency. Dr. Chey and his colleagues previously reported results from a phase 2 study of tenapanor (Am J Gastroenterol. 2017 Feb;112[2]:763-74), and from a phase 3 study with 606 patients reported at a meeting in late 2017. Results from these two studies were similar to those from the new study.

The current study, A 26-Week Study to Evaluate the Efficacy and Safety of Tenapanor in IBS-C (T3MPO-2) enrolled 593 patients at 114 U.S. centers. Enrolled patients met the Rome III criteria for IBS-C and had an average CSMB frequency of less than 3/week. The researchers treated and followed patients for 26 weeks, although the primary endpoint occurred after 12 weeks on treatment, and 481 of the enrolled patients remained in the study through 26 weeks. At baseline, patients had an average of 0.12 CSBM/week and an average abdominal pain score of 6.26, indicative of moderate to severe abdominal pain. These characteristics identified the enrolled patients as being "on the more severe spectrum of what we see in clinical practice," Dr. Chey noted.

Secondary endpoints included the combined endpoint with the target rate of CSBM achieved in at least 9 of the first 12 weeks, 18% on the active drug and 5% on placebo, and in at least 13 of the 26 weeks on treatment, 36% on tenapanor and 24% on placebo. After 26 weeks on treatment, 55% of patients on tenapanor rated themselves as quite satisfied or very satisfied with their treatment, compared with 33% of the placebo-control patients.

T3MPO-2 was funded by Ardelyx, the company developing tenapanor. Dr. Chey has been a consultant to and has received research funding from Ardelyx and from several other companies. A coauthor on the study was an Ardelyx employee.

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Web portal doesn't reduce phone calls or office visits

BY IAN LACY
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Inflammatory bowel disease patients may love web-based portals that allow them to interact with their doctors and records, but it does not seem to reduce their trips to the doctor.

"There was actually no decrease in office visits or phone encounters with patients that are utilizing MyChart [a web-based patient portal]," said Alexander Hristov, MD, a resident at the University of Wisconsin–Madison, in a video interview at the annual Digestive Disease Week®. "So in fact, the patients that had MyChart use were also the patients that were calling in more frequently and visiting the clinic more frequently, which is interesting because we did not see that there was an offset for emergency room visits or hospitalizations."

Out of the 616 total patients with either Crohn's disease (355 patients) or ulcerative colitis (261 patients) analyzed in the study, 28% used MyChart. Those that used MyChart messaging had significantly higher number of office visits and phone encounters ($P = .0001$), compared with non-MyChart users. MyChart users also had higher number of prednisone prescriptions, compared with nonusers (51.9% vs. 40.8%, $P = .01$). There was no difference between MyChart users and nonusers for emergency room visits ($P = .11$) or hospitalizations ($P = .16$).

Most messages sent via MyChart were for administrative reasons (54%), with both symptoms (28%) and education (18%) lagging behind.

Even though patients seem to like the portal, there is no billable time set aside for physicians to add the data for patients to access or respond to patient comments and requests through the portal. Unless MyChart can be shown to improve outcomes in some way, it is only an added burden for physicians.

Dr. Hristov mentioned that further work should be done to understand how web-based portals like MyChart can help both doctors and patients utilize this technology.

"We want to see the actual, measurable clinical outcomes of MyChart use," he said. "So we want to set up a protocol where we can actually have measurable statistics looking at disease activity, inflammatory markers, and is there an impact that we are having on the patients disease course."

Dr. Hristov had no disclosures.

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SOURCE: Hristov A et al. Gastroenterology. 2018 May. doi: 0.1016/S0016-5085(18)32737-9.

CDC concerned about multidrug-resistant *Shigella*

BY CHRISTOPHER PALMER
MDedge News

The Centers for Disease Control and Prevention have issued follow-up recommendations for managing and reporting *Shigella* infections because of concerns about increasing antibiotic resistance and the possibility of treatment failures.

Isolates with no resistance to quinolone antibiotics have ciprofloxacin minimum inhibitory concentration (MIC) values of less than 0.015 mcg/mL. However, the CDC has continued to identify isolates of *Shigella* that, while still within the susceptible range for the fluoroquinolone antibiotic ciprofloxacin (that is, having MIC values less than 1 mcg/mL), have MIC values for ciprofloxacin of 0.12-1.0 mcg/mL, thus appearing to harbor one or more resistance mechanisms. Furthermore, the CDC has identified an increasing number of isolates that have MIC values for azithromycin exceeding the epidemiologic cutoff value, which suggests some form of acquired resistance.

The recommendations advise that, if clinicians need to use antibiotics to treat patients who have *Shigella* infections, they should monitor these patients carefully. In the case of an apparent treatment failure for *Shigella* with either fluoroquinolone or azithromycin, an infectious disease specialist should be contacted to ascertain alternative treatments, and treatment failure information should be reported to the CDC in coordination with local health department. In addition, a stool specimen should be collected for culture; further susceptibility testing should be undertaken, and the isolate should be expedited to the state public health laboratory, which also should notify the CDC to coordinate additional testing.

"CDC is particularly concerned about people who are at high risk for multidrug-resistant *Shigella* infections and are more likely to require antibiotic treatment, such as men who have sex with men, patients who are homeless, and immunocompromised patients. These patients often have more severe disease, prolonged shedding, and recurrent infections," the recommendations stated.

More information can be found in the CDC's Health Alert Network release.

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App monitoring improves quality of IBD care

BY MITCHEL L. ZOLER
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Patients with inflammatory bowel disease who used a smartphone app designed to monitor their clinical status showed significant improvements in their quality of care in a single-center randomized study with 320 patients.

MITCHEL L. ZOLER/MDEDGE NEWS

Home monitoring is "feasible with high adoption, said Dr. Ashish Atreja.

Based on this success, the app will soon be made available to all of the roughly 5,000 inflammatory bowel disease (IBD) patients managed at Mount Sinai Medical Center in New York as well as IBD patients at several other North American centers that plan to adopt the app, Ashish Atreja, MD, said at the annual Digestive Disease Week.®

Home monitoring of IBD patients "is feasible with high adoption," said Dr. Atreja, a gastroenterologist at Mount Sinai in New York who directs the Sinai AppLab. The 162 IBD patients randomized to regularly use the HealthPROMISE app had their quality-of-care metric rise from 50% at baseline to 84% after an average follow-up of 575 days (19 months), a statistically significant improvement over the 158 control patients whose metric rose from 50% to 65% for the study's primary endpoint, he reported. The results also showed a trend toward improved quality of life among the patients using the HealthPROMISE app, compared with the controls, who used an IBD educational app that produced less patient engagement than did the HealthPROMISE app, Dr Atreja said.

Dr. Atreja and his associates modeled the app on remote monitoring methods developed for patients with other types of chronic disease, such as diabetes and heart failure.

"You can't provide proactive IBD care without remote monitoring," Dr. Atreja explained in a video interview. "Reactive care is not best practice anymore. The only way to do treat-to-target is with remote monitoring."

Care coordinators monitor the entries that IBD patients send in via the app. Dr. Atreja estimated that about five care coordinators will be able to track the inputs from the roughly 5,000 IBD patients at Mount Sinai who will soon begin using the app. The financial feasibility of this approach depends in part on the $45/patient per month reimbursement that U.S. health insurers now provide to centers that run remote monitoring programs, he said.

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SOURCE: Atreja A et al. Digestive Disease Week 2018, Abstract 17.

AGA CPU: Extraesophageal symptoms attributed to GERD

BY AMY KARON
MDedge News

When patients lack typical symptoms of gastroesophageal reflux disease (GERD) and have extraesophageal symptoms, ENT, allergy, and pulmonary work-ups are "essential and often should be performed initially," experts note in an American Gastroenterological Association clinical practice update.

Extraesophageal symptoms often are unrelated to GERD or are multifactorial, wrote Michael F. Vaezi, MD, PhD, of Vanderbilt University Medical Center in Nashville, Tenn., and his associates in Clinical Gastroenterology and Hepatology. Gastroenterologists often are asked to look for reflux as the cause of extraesophageal symptoms before other etiologies have been ruled out.

Proposed extraesophageal manifestations of GERD range from chronic throat clearing and dysphonia to otitis, pulmonary fibrosis, laryngeal cancer, and even lung transplant rejection. Stronger evidence links GERD with symptoms of asthma, cough, and hoarseness, the experts note. "When less stringent criteria are used, the attributions are broader and could include sore throat, sinusitis, ear pain, and pulmonary fibrosis."

When asked to assess whether GERD is causing extraesophageal symptoms, consider the "constellation" of patient presentation, test results, and treatment response, according to the clinical practice update. No diagnostic tests "unequivocally link any suspected extraesophageal symptom to GERD." For patients who have both extraesophageal symptoms and typical symptoms of GERD, the authors suggest an evaluator regimen of 6-8 weeks of empiric, aggressive (twice-daily) proton pump inhibitor (PPI) therapy. If aggressive acid suppression therapy appears to improve extraesophageal symptoms, patients should be titrated to the lowest effective treatment dose.

If symptoms persist despite an aggressive trial of a PPI, and patients have a body mass index under 25, and a seemingly low probability of GERD, then the experts recommend pH testing "off" therapy and seeking other etiologies for extraesophageal symptoms. If symptoms persist and a patients' BMI exceeds 25 with a high suspicion of GERD, they recommend evaluations for concomitant asthma or lung disease. If these work-ups are positive, they recommend multichannel intraluminal impedance testing or pH monitoring on treatment.

The clinical practice update strongly discourages surgical treatment of extraesophageal GERD symptoms except in specific populations, such as when patients have objective signs of treatment-refractory GERD and have not responded to comprehensive therapy for other possible causes of extraesophageal symptoms. Recent data suggest that surgery can benefit patients with confirmed structural defects, such as hiatal hernia, which are causing symptomatic, volume-based regurgitation, the experts note. Ideally, these patients should first undergo pH and impedance monitoring to objectively measure the effects of reflux. Additionally, surgical fundoplication "might be beneficial" for patients whose extraesophageal symptoms clearly have responded to PPI therapy but who refuse long-term PPI therapy or who develop unacceptable side effects.

The practice update also extensively discusses the role of testing to evaluate the role of GERD in extraesophageal symptoms. Barium esophagography is insensitive for GERD and is useful only for evaluating dysphagia and the size and type of a hiatal hernia, the experts note. Abnormal laryngoscopy or pharyngoscopic findings are more useful but should not be the "initial driving force" behind a GERD diagnosis and do not necessarily link GERD to extraesophageal symptoms. Likewise, esophagogastroduodenoscopy can identify esophagitis, which signifies GERD but does not establish it as etiologic.

Positive ambulatory pH or impedance monitoring or pharyngeal pH tests also do not definitively link reflux to suspected extraesophageal symptoms, the experts note. They suggest considering "on" therapy monitoring to evaluate treatment efficacy and to time reflux events relative to symptoms in patients with esophagitis, Barrett's esophagus, or a large hiatal hernia. Conversely, they recommend considering "off" treatment testing to rule out GERD in patients who have no history of confirmed or suspected reflux and who have not responded to PPI therapy.

Novel tests, such as salivary pepsin and mucosal impedance, have "no clear role in establishing GERD as the cause of extraesophageal symptoms," the experts emphasize. Clinician scientists also debate the exact pathophysiology of extraesophageal GERD sequelae. While chronic exposure to gastric refluxate clearly can harm proximal structures such as the pharynx, larynx, and bronchial tree, it remains unclear how much acid is necessary to cause injury and whether bile, pepsin, or neurogenic stimulation play a role.

Dr. Vaezi reported having no conflicts of interest. Senior author Frank Zerbib, MD, PhD, reported receiving devices for research purposes from Medtronic and Sandhill Scientific.

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SOURCE: Vaezi MF et al. Clin Gastroenterol Hepatol. 2018 Feb 7. doi: 10.1016/j.cgh.2018.02.001.

CLINICAL CHALLENGES AND IMAGES

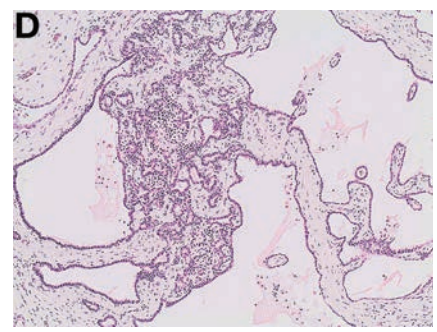
The diagnosis

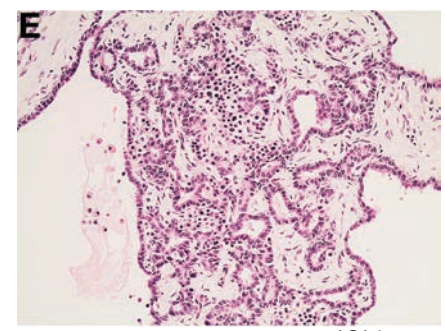
Answer to "What is your diagnosis?" on page 15: Polycystic pancreas

Cross-sectional imaging revealed the diagnosis of polycystic pancreas (diffuse cystic degeneration of the whole organ) with giant cysts in the head and multiple cysts across the whole organ in the absence of concomitant kidney or liver cysts (Figures A, B).

The patient underwent an endoscopic ultrasound-guided fine-needle aspiration before the operation, and a mucinous cystic neoplasm was documented. A total duodenopancreatosplenectomy followed. The postoperative course was uneventful. Histology showed multiple cysts of variable diameter lined by monolayer flattened or cuboidal epithelium without atypia and confirmed the diagnosis of polycystic pancreas (Figures D, E; stain: hematoxylin and eosin; original magnifications: ×100 and ×200, respectively). Genetic testing was negative for von Hippel–Lindau (VHL) disease. The patient remains in good general condition under diabetes management and oral administration of pancreatic enzymes 45 months after pancreatectomy. Magnetic resonance imaging of the central nervous system and abdomen were without pathologic findings.

Although pancreatic cysts are very common, a diffuse cystic degeneration of the pancreas in the form of polycystic pancreas is very infrequent and has been described in patients with VHL disease.[1] It is almost always associated with multiple renal cysts.[1] Genetic testing for VHL disease is suggested in all cases presenting with multiple pancreatic cysts by some investigators.[2] It has an accuracy greater than 80%, which reaches 95%-100% in patients who fulfill the clinical criteria for VHL disease.[3]





AGA Institute

The novelty of this case is double; to the best of our knowledge, polycystic pancreas with such a volume (cysts up to 25 cm) has not yet been documented in the literature and has not been at all described in the absence of VHL disease up to now.

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Hemostatic clipping cuts bleeds after polyp removal

BY MITCHEL L. ZOLER
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Using hemostatic clips to close colonic mucosal defects following endoscopic removal of larger polyps cut the rate of delayed, severe bleeding episodes in half in a multicenter, randomized trial with 918 patients.

"The benefit appears limited to proximal polyps," Heiko Pohl, MD, said at the annual Digestive Disease Week.® In that prespecified subgroup, which included two-thirds of enrolled patients, placement of hemostatic clips on defects left after removing polyps 20 mm in diameter or larger cut the rate of delayed, severe bleeding by two-thirds, compared with patients with large defects not treated with clips. This result represented a number needed to treat with clips of 15 patients with large proximal polyps to prevent one episode of delayed severe bleeding, said Dr. Pohl, a gastroenterologist at the VA Medical Center in White River Junction, Vt.

Although the results that Dr. Pohl reported came from a trial that originally had been designed to generate data for Food and Drug Administration approval for using the clips to close defects following large polyp removal, the clips received approval for this indication from the agency in 2016 while the study was still in progress.

But Dr. Pohl maintained that the new evidence for efficacy that he reported will provide further impetus for gastroenterologists to use clips when they remove larger polyps in proximal locations. "I think this study will help standardize treatment of mucosal resections and change clip use," he said in an interview.

"This was a terrific study, and one that needed to be done," commented John R. Saltzman, MD, professor of medicine at Harvard Medical School and director of endoscopy at Brigham and Women's Hospital in Boston. But Dr. Saltzman, who spoke from the floor during discussion of Dr. Pohl's report, added that data on the average number of clips required to close defects were needed to assess the cost-effectiveness of the treatment, data that Dr. Pohl said were available but still being analyzed.

"We have to know how many clips to use and how to close the polyp," Dr. Saltzman said. Dr. Pohl

MITCHEL L. ZOLER/MDEDGE NEWS

"The benefit appears limited to proximal polyps," said Dr. Heiko Pohl.

estimated that roughly four or five clips had been used per defect, but he cautioned that this estimate was preliminary pending his complete analysis of the data.

The CLIP (Clip Closure After Endoscopic Resection of Large Polyps) study enrolled patients with at least one nonpedunculated colonic polyp that was at least 20 mm in diameter at 16 U.S. centers, as well as 1 center in Montreal and 1 in Barcelona. The patients averaged 65 years of age, and 6%-7% of patients had more than one large polyp removed during their procedure. Randomization produced one important imbalance in assignment: 25% of the 454 patients in the clipped arm were on an antithrombotic drug (either an anticoagulant or antiplatelet drug) at the time of their endoscopy, compared with 33% of the 464 patients in the control arm.

The study's primary endpoint was the incidence of "severe" bleeding within 30 days after the procedure. The study defined severe bleeding as an event that required hospitalization, need for repeat endoscopy, need for a blood transfusion, or need for any other major intervention, explained Dr. Pohl, who is also on the staff of Dartmouth-Hitchcock Medical Center in Lebanon, N.H.

Such events occurred in 3.5% of the patients who underwent clipping and in 7.3% of control patients who received no clipping, a statistically significant difference ($P = .01$). Among patients with proximal polyps, the bleeding rates were 3.3% among clipped patients and 9.9% among controls, also a statistically significant difference. Among patients with distal polyps the bleeding rates were 4.0% among clipped patients and 1.4% among controls, a difference that was not statistically significant.

Dr. Pohl and his associates ran three other prespecified, secondary analyses that divided the enrolled patients into subgroups. These analyses showed no significant effect on outcome by polyp size when comparing 20- to 39-mm polyps with polyps 40 mm or larger, treatment with an antithrombotic drug, or method of cauterization. The median time to severe bleeding was 1 day among the controls and 7 days among the clipped patients.

Aside from the difference in rates of delayed bleeding, the two study arms showed no significant differences in the incidence of any other serious postprocedure events. The rates of these nonbleeding events were 1.3% among clipped patients and 2.4% among the controls.

The researchers ran all these analyses based on the intention-to-treat assignment of patients. However, during the study, 9% of patients assigned to the control arm crossed over and ended up receiving clips during their procedure after all, a rate that Dr. Pohl called "surprisingly high," whereas 14% of patients assigned to the clip arm never received clips. A per-protocol analysis that censored patients who did not receive their assigned treatment showed that, among the remaining patients who underwent their assigned treatment, the rate of delayed, severe bleeds was 2.3% among the 390 patients actually treated with clips and 7.2% among the 419 controls who never received clips, a statistically significant difference, he reported.

Dr. Pohl also noted that it was "somewhat surprising" that clipping appeared to result in complete closure in "only" 68% of patients who underwent clipping and that it produced partial closure in an additional 20% of patients, with the remaining patients having mucosal defects that were not considered closed by clipping.

The study was funded by Boston Scientific, the company that markets the hemostatic clip (Resolution 360) tested in the study. Dr. Pohl had no additional disclosures. Dr. Saltzman had no disclosures.

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SOURCE: Pohl H et al. Digestive Disease Week 2018, Presentation 886.

Better to start younger?

Screening *from page 1*

potential years of life saved, addresses anticipated rising incidence going forward, and is expected to contribute to the reduction in disparities in incidence before age 50 years in some racial groups," the ACS guideline authors added.

The recommendation to start screening at age 45 is a "qualified" recommendation, the authors said, given the limitations of the current evidence base. Most studies to date have been focused on older individuals, in keeping with long-standing recommendations to start screening at age 50.

The move downward in screening age recommendation acknowledges one of the most "significant and disturbing" developments in CRC, the guideline's authors said: the marked increase in incidence among younger individuals.

While CRC incidence and mortality have been declining in adults aged 55 years and older, recent studies cited in the ACS guideline document show a 51% increase in incidence from 1994 to 2014 – and an 11% increase in mortality from 2005 to 2015 – for adults younger than 55 years.

The current age-specific incidence rate for adults 45-49 years is 31.4 per 100,000, compared with 58.4 per 100,000 in adults 50-54 years. However, the ACS guideline authors said the higher rate in the older cohort is partly influenced by more frequent screening. "The true underlying risk in adults aged 45-49 years is likely closer to the risk in adults aged 50-54 years than the most recent age-specific rates would suggest," they wrote.

Since patients in this age range have not been routinely screened before, the ACS recommendation is based on modeling. Now we need to analyze the outcomes of early screening to identify which patients will benefit most.

Choices for screening include either a structural examination or a high-sensitivity stool-based test, according to the guideline, which doesn't state a preference for any particular test.

The AGA, in their statement in response, noted that, with CRC rates rising in people younger than age 50, it is appropriate to consider beginning routine screening at age 45. The statement continues "Since patients in this age range have not been previously routinely screened, the ACS recommendation is based on modeling. Now we need to analyze the outcomes of early screening to identify which patients will benefit most."

In addition to Dr. Wolf, members of the ACS Guideline Development Group received no compensation.

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SOURCE: Wolf AMD et al. CA Cancer J Clin. 2018 May 30. doi: 10.3322/caac.21457.

PERSPECTIVE

ACS recommends going low

The latest recommendations from the American Cancer Society added individuals 45 years and older to the population for whom CRC screeningshould be performed. The change from a start age of 50 was prompted by the increase in CRC reported in younger adults and was based on a computer simulation that predicted a greater number of life-years saved using an earlier age for initiation of screening among adults at average risk for development of colorectal cancer. It is likely that screening will reduce cancer mortality even in this younger age group; however, several issues should be considered when implementing this policy.

Differences in screening tests: The reason for the increase in CRC in younger adults is not known. Nor is it understood why this increase is far greater for rectal cancer than cancers more proximal in the colon. Based on this observation, however, it is possible that flexible sigmoidoscopy may be a more appropriate test than colonoscopy for younger adults. Conversely, we do not know if the precursor of early-age CRC is more likely to be a flat lesion that is more difficult to detect using endoscopy, or less likely to bleed that may make FIT less able to detect, or have a genetic mechanism different from proximal CRC that is not part of the current DNA stool testing.

The evidence supporting screening tests are not equal. No randomized trial confirming the effectiveness of screening colonoscopy to reduce CRC mortality has been completed, although at least four studies are ongoing. More importantly, a recent study of one-time screening flexible sigmoidoscopy published in JAMA reported a significant reduction in CRC incidence and mortality among men that was not seen among women. A variety of factors may have caused this observation, one of which is that the age-related incidence of CRC among women is lower compared with men. One-time screening will prevent fewer cancers in women since the majority of cancers precursors have not developed at a younger age. Starting screening at age 45 years may miss even more cancers among women.

Value is the benefit gained with screening compared with the resources required to implement screening. The value of screening is greater in older individuals than in younger individuals because the risk of CRC is increased and for this reason, population-based screening should focus on screening older adults who have not undergone screening. Unfortunately, U.S. population adherence to CRC screening remains below 70% with little improvement since 2010. Only after the older population is fully screened should our attention shift to younger populations.

Disparities: The individuals most likely to undergo screening are unlikely to be the individuals most likely to benefit. African Americans have a higher age-related incidence of CRC but have the lowest screening rates in the U.S. compared with other racial and ethnic groups. This relates to not only reduced access but also reduced utilization. It is a concern that, by increasing the pool of individuals recommended for screening, we may also reduce access to those who may benefit most.

The ACS recommendations to go low may reduce colorectal cancer mortality in younger adults; however, our lack of understanding about the biology of the cancer hampers our ability to recommend the optimal screening strategy, sacrifices value, and may increase disparities in cancer outcomes.

John M. Inadomi, MD, AGAF, is a Cyrus E. Rubin Professor of Medicine and head of the division of gastroenterology at the University of Washington School of Medicine, Seattle. He has no conflicts.

CRC recurrence surveillance: No benefit to intense strategy

BY ANDREW D. BOWSER
MDedge News

More frequent follow-up with computed tomography of the thorax and abdomen and serum carcinoembryonic antigen (CEA) testing does not significantly improve mortality rates or improve time to detection of recurrence, results of two studies in JAMA have suggested.

In COLOFOL, a randomized clinical trial of more than 2,500 patients with stage II or III colorectal cancer, more frequent follow-up with CT of the thorax and abdomen and serum CEA did not significantly improve 5-year overall mortality or colorectal cancer–specific mortality rates.

In the second study, a retrospective cohort analysis of the National Cancer Database (NCDB) including more than 8,500 patients with stage I-III colorectal cancer, investigators found no significant association between the surveillance testing frequency and time to detection of disease recurrence.

The COLOFOL randomized trial, reported by Henrik T. Sørensen, DMSc, head of the department of clinical epidemiology at Aarhus (Denmark) University Hospital, and his colleagues, included 2,509 patients with stage II or III colorectal cancer who were randomized either to a high-frequency group, in which CT and CEA testing were conducted at 6, 12, 18, 24, and 36 months after surgery, or to a low-frequency group that received testing only at 12 and 36 months after surgery.

The 5-year colorectal cancer–specific mortality rate was similar: 10.6% for the high-frequency follow-up group versus 11.4% for the low-frequency group (risk difference, 0.8%; 95%confidence interval, –1.7% to 3.3%; *P* = .52). Likewise, 5-year overall mortality was 13.0% for the high-frequency group and 14.1% for the low-frequency follow-up groups (risk difference, 1.1%; 95% CI, –1.6% to 3.8%; *P* = .43). High-intensity testing did result in recurrences being detected earlier, but it did not translate into a reduced mortality rate.

The retrospective NCDB analysis, reported by George J. Chang, MD, of University of Texas MD Anderson Cancer Center, Houston, and his coauthors, included 8,529 patients with stage I-III colorectal cancer treated at 1,175 facilities.

Facilities designated as high intensity for imaging performed a mean of 2.87 imaging tests over 3 years, compared with 1.63 for facilities designated as low intensity. Median time to detection of recurrence was similar, at 15.1 months for patients treated at centers with high-intensity surveillance versus 16.0 months for those treated at low-intensity centers (hazard ratio, 0.99; 95% CI, 0.90-1.09). High-intensity CEA testing facilities performed a mean of 4.31 tests within 3 years versus 1.63 for low-intensity facilities. Again, investigators found similar median time to detection of recurrence for high- and low-intensity facilities (15.9 months versus 15.3 months, respectively; hazard ratio, 1.00; 95% CI, 0.90-1.11)

The only disclosures were one investigator in the COLOFOL trial who reported potential conflicts of interest with Janssen-Cilag and Merck Serono, and one coauthor in the NCDB study who reported a potential conflict of interest related to Johnson & Johnson.

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SOURCES: Sørensen HT et al. JAMA. 2018 May 22. doi: 10.1001/jama.2018.5623; Chang GJ et al. JAMA. 2018 May 22. doi; 10.1001/jama.2018.5816.

Four drugs on the horizon

Trials *from page 1*

liver histology, compared with 21% of patients on placebo.

The REGENERATE trial is evaluating the effects of obeticholic acid on histologic improvement and liver-related outcomes in NASH patients. Patients have been randomized to 10 mg of OCA, 25 mg of OCA, or placebo. No results have been posted.

DR. HARRISON

As he did for trials involving OCA, Dr. Harrison detailed the results of a phase 2b elafibranor study that led to a registration trial now underway. In Golden 505 (Phase IIb Study to Evaluate the Efficacy and Safety of GFT505 Versus Placebo in Patients With Non-Alcoholic Steatohepatitis), patients were randomized to GFT505 80 mg, GFT505 120 mg, or placebo. The study's aim was to identify the percentage of responders with disappearance of steatohepatitis without worsening of fibrosis. There was no difference between placebo and the treatment groups for this outcome, but a post hoc analysis revealed that NASH resolved in a higher proportion of the 120-mg elafibranor group, vs. the placebo group (19% vs. 12%, respectively). This translated into a reduction of 0.65 in liver fibrosis stages in responders, compared with a 0.10 increase in nonresponders (*P* less than .001).

Elafibranor is being further examined in RESOLVE-IT (Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis), but no results were posted at press time.

Cenicriviroc has followed a similar path, with a phase 2b leading to a phase 3 study. CENTAUR (Efficacy and Safety Study of Cenicriviroc for the Treatment of NASH in Adult Subjects With Liver Fibrosis) looked at histologic improvement in NAFLD over 2 years. Patients were randomized to cenicriviroc 150 mg (group A) or two placebo arms (groups B and C) for the first year. In the second year, patients in placebo group B started to receive 150 mg cenicriviroc and group C remained as the placebo until the end of year 2. NAFLD activity scores were similar between placebo and cenicriviroc. But fibrosis outcomes were met at a much higher rate in the cenicriviroc group, vs. those seen with placebo (20% vs. 10%, respectively; *P* = .02).

Based on these findings, AURORA (Phase 3 Study for the Efficacy and Safety of Cenicriviroc for the Treatment of Liver Fibrosis in Adults With NASH) is evaluating the safety and efficacy of cenicriviroc for treatment of liver fibrosis in adults with NASH.

Finally, there is selonsertib, an ASK1 inhibitor. A phase 2 trial showed that it had the potential to induce stage reduction in fibrosis at an 18-mg dose. Now there are two phase 3 studies, STELLAR 3 and STELLAR 4, evaluating the effects of selonsertib in adults with NASH and NASH with compensated cirrhosis.

Because of the complexity of NASH and other fatty liver diseases, trials testing therapies for these conditions face unique challenges in the approval process, Dr. Harrison said. "To do those types of studies, it's going to take a long time to get FDA approval," he said. "There's a way to get conditional approval; it's called the Subpart H pathway, and the FDA has accepted a couple reasonable, likely surrogates. One is resolution of NASH without worsening of fibrosis, and you need to know what that definition is: resolution of NASH." This means eliminating inflammation and ballooning rather than worrying about fat on the liver biopsy, he said.

Dr. Harrison sees these four drugs becoming available sometime next year.

Dr. Harrison has received grants from Genfit, Gilead, and Intercept, among others. He consults for Medpace, Innovate Biopharmaceuticals, and other companies, and is on the speakers bureau for Alexion Pharmaceuticals and AbbVie.

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SOURCE: Harrison S. Digestive Disease Week 2018, Presentation 2230.

Percutaneous procedure gives alternative to anticoagulation

BY MITCHEL L. ZOLER
MDedge News

REPORTING FROM DDW 2018

WASHINGTON – Catheter-directed clot lysis and thrombectomy with creation of a bypass shunt is a reasonable alternative to prolonged anticoagulation for treating patients with portal vein thrombosis (PVT) based on the accumulated reported experience since 1993 using this percutaneous treatment.

Use of a transjugular intrahepatic portosystemic shunt (TIPS) for treating PVT "is feasible and effective in achieving a significant and sustainable reduction in clot burden with a low risk of major complications," Nelson Valentin, MD, said at the annual Digestive Disease Week.® "TIPS should be considered a viable treatment option for patients with PVT," said Dr. Valentin, a gastroenterology fellow at Mount Sinai Beth Israel hospital in New York.

His systematic review of the literature identified 18 case series published during 1993-2016 that included a total of 439 patients who underwent TIPS. Analysis of the accumulated data showed that operators performed TIPS with technical success in 87% of these reported cases, achieved at least partial recanalization of portal outflow in 84% of patients, and produced complete recanalization in 74%. The average reported change in portal vein pressure was a reduction of 14.5 mm Hg, and the major adverse effect was hepatic encephalopathy, which occurred in a quarter of patients but generally resolved without sequelae. No patients died as a result of undergoing the procedure.

"There is sufficient evidence from these reports to at least consider TIPS as an adjunct to anticoagulation or perhaps as primary therapy," especially for patients with PVT who have a contraindication for anticoagulation, Dr. Valentin said in an interview. Standard anticoagulation for PVT would today involve acute treatment with a low-molecular-weight heparin followed by oral anticoagulation for a total treatment time of at least 6 months and continued for a year or longer in some patients. A recently published review of reported experience using anticoagulation to treat PVT found a complete recanalization rate of 41% and a complete or partial rate

Continued on following page

PRACTICE MANAGEMENT TOOLBOX: Current, future applications of telemedicine to optimize chronic liver disease care

BY MARINA SERPER MD, MS, AND MICHAEL L. VOLK, MD, MSC, AGAF

Over the past several decades, as the use of wireless broadband technology has become more advanced and cellphone and internet use has become nearly ubiquitous, there has been a rapid emergence of technological modalities to facilitate health care delivery at a distance. The various forms of telemedicine currently in use are described in Table 1. Any of these can be provided as synchronous, such as a video teleconference with a clinician, or asynchronous/store-and-forward, which may encompass review of prerecorded data such as clinical information through an electronic consultation, or of pathology and/or radiology images.

Recent studies have shown that telehealth interventions are effective at improving clinical outcomes and decreasing inpatient utilization, with good patient satisfaction in the areas of mental health and chronic disease management. Despite the

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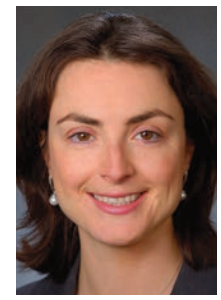

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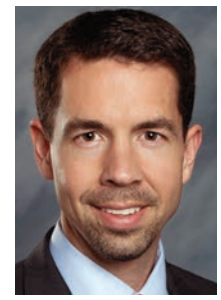

DR. VOLK

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of 66%, which suggests that TIPS is at least as effective, although Dr. Valentin cautioned that no reported study has directly compared the two alternative approaches. A study designed to make this direct comparison is warranted by the reported results using TIPS, Dr. Valentin said. And the experience with TIPS positions it as an option for patients who do not respond to anticoagulation or would prefer an alternative to prolonged anticoagulation.

One factor currently limiting use of TIPS, which is usually performed by an interventional radiologist, is that the procedure is technically demanding, with a limited number of operators with the expertise to perform it. If TIPS became more widely accepted as an option for treating PVT, then the pool of interventionalists experienced with performing the procedure would grow, Dr. Valentin noted.

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SOURCE: Valentin N et al. Digestive Disease Week, Presentation 361.

Drugmakers blamed for blocking generics have cost U.S. $

BY SYDNEY LUPKIN, KAISER HEALTH NEWS

Makers of brand-name drugs called out by the Trump administration for potentially stalling generic competition have hiked their prices by double-digit percentages since 2012 and cost Medicare and Medicaid nearly $12 billion in 2016, a Kaiser Health News analysis has found.

The Food and Drug Administration listed more than 50 drugs whose manufacturers have withheld or refused to sell samples and cited 164 inquiries for help obtaining them. Thirteen of these pleas from makers of generics pertained to Celgene's blockbuster cancer drug Revlimid (lenalidomide), which accounted for 63% of Celgene's revenue in the first quarter of 2018, according to a company press release.

The brand-name drug companies "wouldn't put so much effort into fighting off competition if these weren't [such] lucrative sources of revenue," said Ameet Sarpatwari, JD, PhD, of Harvard Medical School in Boston. "In the case of a blockbuster drug, that can be hundreds of millions of dollars of revenue for the brand-name drugs and almost the same cost to the health care system."

Indeed, a KHN analysis found that 47 of the drugs cost Medicare and Medicaid almost $12 billion in 2016. The spending totals don't include rebates, which drugmakers return to the government after paying for the drugs upfront but are not public. The rebates ranged from 9.5% to 26.3% for Medicare Part D in 2014, the most recent year that data are available.

By delaying development of generics, drugmakers can maintain their monopolies and keep prices high. Most of the drugs cost Medicare Part D more in 2016 than they did in 2012, for an average spending increase of about 60% more per unit. This excludes drugs that don't appear in the 2012 Medicare Part D data.

Revlimid cost Medicare Part D $2.7 billion in 2016, trailing only Harvoni (ledipasvir and sofosbuvir), which treats hepatitis C and is not on the FDA's new list. The cost of Revlimid, which faces no competition from generics, has jumped 40% per unit in just 4 years, the Medicare data show, and cost $75,200/beneficiary in 2016.

Some drugs on the FDA's list, including Celgene's, are part of a safety program that can require restricted distribution of brand-name drugs that have serious risks or addictive qualities. Drugmakers with products in the safety program sometimes say they can't provide samples unless the generics manufacturer jumps through a series of hoops "that generic companies find hard or impossible to comply with," Dr. Gottlieb said in a statement.

The Department of Health & Human Services Office of Inspector General issued a report in 2013 that said the FDA couldn't prove that the program actually improved safety, and Dr. Sarpatwari said there's evidence drugmakers are abusing it to stave off competition from generics.

Dr. Gottlieb said the FDA will be notifying the Federal Trade Commission about pleas for help from would-be generics manufacturers about obtaining samples, and he encouraged the manufacturers to do the same if they suspect they're being thwarted by anticompetitive practices.

Celgene spokesman Greg Geissman said the company has sold samples to generics manufacturers and will continue to do so. He stressed maintaining a balance of innovation, generic competition, and safety.

The highest number of pleas for help related to Actelion Pharmaceuticals' pulmonary hypertension drug Tracleer (bosentan). In 2016, that drug cost Medicare $90,700/patient and more than $304 million overall. Meanwhile, spending per unit jumped 52% from 2012 through 2016.

PhRMA, the trade group for makers of brand-name pharmaceuticals, said the FDA's list was somewhat unfair because it lacked context and responses from those it represents.

Congress is considering the CREATES Act, which stands for "Creating and Restoring Equal Access to Equivalent Samples" and would foster competition in part by allowing generics manufacturers to sue brand-name drug manufacturers to compel them to provide samples.

The bill's sponsor, Sen. Patrick Leahy (D-Vt.), said more transparency from the FDA is helpful, but more work from the agency is needed to end the anticompetitive tactics. "With billions of dollars at stake, a database alone will not stop this behavior," Sen. Leahy said.

Cosponsor Sen. Chuck Grassley (R-Iowa), chairman of the Judiciary Committee, expressed similar sentiments, telling KHN: "The CREATES Act is necessary because it would serve as a strong deterrent to pharmaceutical companies that engage in anticompetitive practices to keep low-cost generic drugs off the market."

The FDA hasn't come out in support of CREATES. "They should know that this is going to require a legislative solution," Dr. Sarpatwari said. "Why are they not stepping into this arena and saying that?"

KHN's coverage of prescription drug development, costs, and pricing is supported by the Laura and John Arnold Foundation. Kaiser Health News is a nonprofit national health policy news service. It is an editorially independent program of the Henry J. Kaiser Family Foundation that is not affiliated with Kaiser Permanente.

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increased uptake, significant infrastructure and legal barriers to telemedicine remain and the literature regarding its utility in clinical practice continues to emerge. Compared with other chronic diseases (e.g., heart failure, diabetes, mental illness) there is a dearth of literature on the use of telemedicine in liver disease.

Use of telemedicine in chronic liver disease: A literature review

We performed a systematic review of telemedicine in chronic liver disease. In consultation with a biomedical librarian, we searched for English-language articles for relevant studies with adult participants from July 1984 to May 2017 in PubMed, OVID Medline, American Association for the Study of Liver Disease, EMBASE, Web of Science, ClinicalTrials.gov, Elsevier/Science Direct, and the Cochrane Library (the search strategy is shown in the Supplementary Material at https://doi.org/10.1016/j.cgh.2017.10.004). The references of original publications and of review articles additionally were screened for potentially relevant studies. Supplementary Table 1 (https://doi.org/10.1016/j.cgh.2017.10.004) shows the 20 published articles of telemedicine studies. Among these, there were 9 prospective trials, 3 retrospective studies, 2 case reports, and 6 small case series; 1 of the studies was randomized prospectively, and 10 were uncontrolled.

Telemedicine in hepatitis C treatment

Much of the published literature of telemedicine in liver disease (Supplementary References at https://doi.org/10.1016/j.cgh.2017.10.004) has described the use of video teleconferencing for the management of hepatitis C virus (HCV), both in the era of interferon-based treatment and with new direct-acting antivirals. Several studies in the United States and throughout the world retrospectively evaluated the use of live telemedicine/videoteleconferencing to deliver HCV therapy to incarcerated patients, those living in rural areas, and in the Veterans Affairs using the spoke-and-hub model. Generally, sustained virologic response rates were similar or higher with telemedicine than among patients receiving in-person visits, whereas discontinuation rates were generally low and side effects were well managed. Visits generally were led by nurses or specialty-care physicians and were associated with high patient satisfaction. A randomized study comparing a telephone-based self-management intervention of cognitive-behavioral therapy vs. usual care for 19 veterans undergoing HCV treatment with interferon-based regimens showed that the telephone-based cognitive-behavioral therapy group had lower depression and anxiety symptoms and reported a better quality of life. Several more recent abstracts have described successful use of telemedicine for HCV treatment (Supplementary Table 2 and Supplementary References [https://doi.org/10.1016/j.cgh.2017.10.004]).

One of the most cited examples of telemedicine for HCV has been the Extension for Community Healthcare Outcomes (ECHO), or Project ECHO.[1] This care model initially was designed to increase access to interferon-based treatment for patients with HCV in rural areas of New Mexico. In contrast to previously cited examples in which subspecialty or physician nurses directly provided clinical care in HCV, ECHO targeted frontline primary care providers to enhance expertise and enable problem-based learning via live video teleconferencing. Primary care providers participating in ECHO presented cases to content experts through video-linked knowledge networks; didactic presentations also were developed for provider education. The program has been expanded to Utah and Arizona and showed success with high rates of HCV treatment initiation and sustained virologic response.[2]

As an early adopter of telemedicine and after the success of Project ECHO in 2011, the VA developed and implemented the Specialty Care Access Network–ECHO to increase access and training, and provide real-time expert consultation for primary care physicians in multiple chronic conditions, including HCV and chronic liver disease. Several recent unpublished abstracts in the VA have reported on the use of telemedicine via videoteleconferencing to increase access to hepatology care in cirrhosis with high patient satisfaction.

Telemedicine to aid in procedural/surgical management

A few reports have been published in the use of synchronous video and digital technology to aid in periprocedural management in liver disease. A case report highlighted a successful example of gastroenterologist-led teleproctoring using basic video technology to enable a surgeon to perform sclerotherapy for hemostasis in the setting of a variceal bleed.[3] Another case report described the transmission of smartphone images from surgical trainees to an attending physician to make a real-time decision regarding a possibly questionable liver procurement, which took place 545 km away from the university hospital.[4]

A retrospective case series described the feasibility and successful use of high-resolution digital macroscopic photography and electronic transmission between liver transplant centers in the United Kingdom to increase the utilization of split-liver transplantation, a setting in which detailed knowledge of vessel anatomy is needed for advanced surgical planning.[5] Similarly, an uncontrolled case series from Greece reported on the feasibility and reliability of macroscopic image transmission to aid in the evaluation of liver grafts for transplantation.[6]

Telemedicine to support evaluation and management of hepatocellular carcinoma

One recent abstract reported on the use of asynchronous store-and-forward telemedicine for screening and management of hepatocellular carcinoma and evaluated process outcomes of specialty care access for newly diagnosed patients.[7] A multifaceted approach included live video teleconferencing and centralized radiology review, which was conducted by a multidisciplinary tumor board at an expert hub site, which provided expert opinion and subsequent care (e.g., locoregional therapy, liver transplant evaluation) to spoke sites. As a result, the time to specialty evaluation and receipt of hepatocellular carcinoma therapy decreased by 23 and 25 days, respectively.

Remote monitoring interventions

The literature for remote monitoring in chronic liver disease or after liver transplant currently is emerging. A prospective pilot study by Thomson et al.[8] evaluated the utility of a telephone-based interactive voice response intervention in predicting hospitalizations and death among 79 patients with decompensated cirrhosis. Parameters such as self-reported weakness and more than a 5-pound weight gain in 1 week were associated with increased rates of hospitalization. Ertel et al.[9] recently published results of a nonrandomized pilot study of remote monitoring using smart tablets among 20 liver transplant recipients. Patients were followed up for 90 days after the liver transplant surgery whereby daily weights, blood glucose reading, and vital signs were transmitted to the transplant center; violations of preset thresholds were recorded, although it was not clear whether members of the clinical team were asked to act upon the violations. Readmission rates among patients in the pilot study at 30 and 90 days were 20% and 30%, respectively, compared with 40% and 45% among historical controls. Patients with 100% daily interaction with the smart tablets did not experi-

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Table 1. What is and is not telemedicine

Types of telemedicine	
Televisits	Usual patient-provider visit, but via videoconference
Telesupervision	Midlevel provider or house officer presents to attending in another location (with or without patient present)
Telemonitoring	Signs or symptoms sent electronically from patient to provider team in another location
Teleinterpretation	Remote interpretation of radiology and other tests
Teleconsultation	Provider in one location presents a case to an expert in another location (with or without patient present; e.g., ECHO or remote tumor board)
Not telemedicine	
Remote education	Medical education only, no patient involved
Remote technology used for research (e.g., online questionnaires)	Research, not medicine
Social media	Not traditionally considered as medicine, no patient-provider relationship

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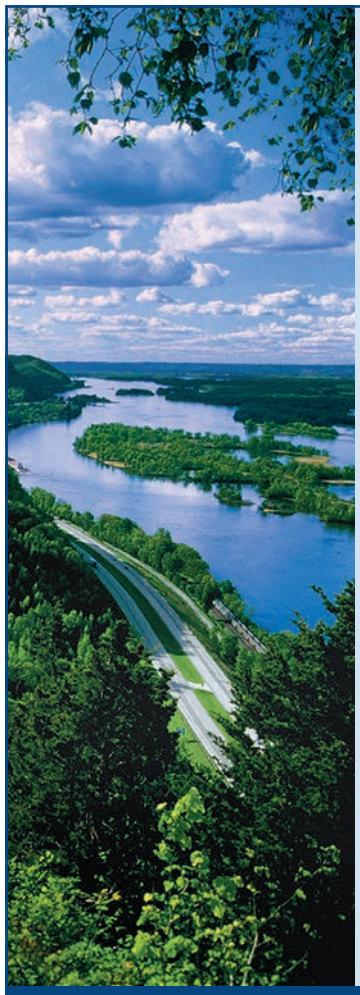

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ence any readmissions.

Another abstract described a nurse-led remote monitoring intervention paired with at-home video teleconference visits among 31 patients with alcoholic cirrhosis.[10] The majority of patients were able to stop alcohol intake, improve their nutrition, and increase physical activity. Supplementary Table 3 (https://doi.org/10.1016/j.cgh.2017.10.004) shows additional ongoing or completed telemedicine interventions in liver disease as obtained from www.clinicaltrials.gov.

Proposed framework for advancing telemedicine in liver disease: The case for more research and policy changes

Telemedicine can serve two main goals in liver disease: improve access to specialty care, and improve care between visits. For the first goal, the technology is straightforward and limited research is required; the main barriers are regulatory and reimbursement. As an example, one of the authors (M.L.V.) uses telemedicine to perform liver transplant evaluations in Las Vegas; Nevada is a state without a liver transplant program. Patients are seen initially by a nurse practitioner who resides in Las Vegas, and those patients needing transplant evaluation are scheduled for a video visit with the attending physician who is physically in California. This works well, and patients love it; however, the business model is dependent on the downstream financial incentive of transplantation. In addition, various regulatory requirements must be satisfied such as monthly in-person visits. For the second goal, a number of exciting possibilities exist such as remote monitoring and patient disease management, but more research is needed.

Research

According to the Pew Research Center, 95% of American adults own a cellphone and 77% own a smartphone. These devices passively gather an extraordinary amount of data that could be harnessed to identify early warning signs of complications (remote monitoring). Another potentially fruitful area of research is patient disease management. This includes using technology (e.g., reminder texts) to effect behavior change such as with medication adherence, lifestyle modification, education, or peer mentoring.

Take-away points

1. Telemedicine can take various forms, such as televisits, telesupervision, teleconsultation (e.g., Project ECHO), and remote monitoring.
2. The main goals of telemedicine in liver disease are to a) improve access, and b) improve care between visits.
3. The role of telemedicine to improve access to specialty care for liver disease has been established; however, additional research is needed to identify the best ways to use telemedicine for improving care between visits.
4. Barriers to widespread adoption of telemedicine are mainly driven by lack of third-party payer reimbursement.

As an example, the coauthor (M.S.) is leading a study to promote physical activity among liver transplant recipients by using an online web portal developed by researchers at the University of Pennsylvania (Way to Health), which interfaces with patient cellphones and digital accelerometer devices. Participants receive daily feedback through text messages with their step counts, and small financial incentives are provided for adequate levels of physical activity. Technology also can facilitate the development of disease management platforms, which could improve both access and in-between visit monitoring, especially in remote areas. One of the authors (M.L.V.) currently is leading the development of a remote disease management program with funding from the American Association for the Study of Liver Diseases.

Despite the tremendous promise, traditional research methods in telemedicine may be challenging given the rapid and increasing uptake of health technology among patients and health systems. As such, the classic paradigm of randomized controlled trials to evaluate the success of an intervention or change in care delivery often is not feasible. We believe there is a need to recalibrate the definition of what constitutes a high-quality telemedicine study. For example, pragmatic trials and those designed within an implementation science framework that evaluate feasibility, scalability, and cost, in parallel with traditional clinical outcomes, may be better suited and should be accepted more widely.[11]

Policy

Even when the technology is available and research shows efficacy, the implementation of telemedicine in clinical practice faces regulatory and reimbursement barriers. The first regulatory question is whether a patient–provider relationship is being established (with the exception of limited provider–provider curbside consultation, the answer usually is yes). If so, the practice then is subject to all the usual regulatory concerns. The provider needs to be licensed at the site of origin (where the patient is located) and hold malpractice coverage for that location, and the video and medical record transmission should be compliant with the Health Insurance Portability and Accountability Act. The next challenge is reimbursement. Medicare pays for video consultation only if the patient lives in a designated rural Health Professional Shortage Area (www.cms.gov), and reimbursement by private payers varies. Even this is dependent on ever-changing state laws. Reimbursement for remote patient monitoring is even more limited (the National Telehealth Policy Research Center publishes a useful handbook: http://www.cchpca.org/sites/default/files/resources/50%20State%20FINAL%20April%202016.pdf). Absent a bipartisan Congressional effort to remedy this situation, the best hope for removing reimbursement barriers lies with payment reform. The Medicare Access and CHIP Reauthorization Act of 2015 mandates that the Centers for Medicare & Medicaid Services shift from fee-for-service to alternative payment models in the coming years. In these alternate payment models, providers are responsible for the overall quality and total cost of care for a population of patients. In this scenario, there may be a financial incentive for telemedicine, especially remote monitoring, to keep patients out of the hospital. Until then, under current payment models, reimbursement is limited and the barriers to widespread implementation are high.

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