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GI & HEPATOLOGY NEWS

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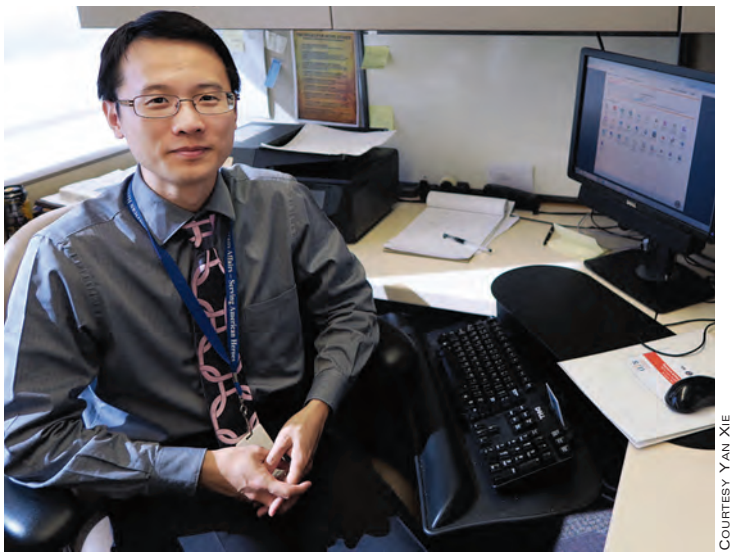

COURTESY YAN XIE

Yan Xie and coauthors found increased mortality in a large group of veterans who used PPIs and were followed for more than 5 years.

Increased risk of death seen in PPI users

BY BIANCA NOGRADY
Frontline Medical News

Proton pump inhibitors (PPIs) are associated with a significantly higher risk of death than are H_2-receptor antagonists, according to a 5-year longitudinal cohort study.

The study, published online in BMJ Open, found that increased risk of death was evident even in people without gastrointestinal conditions, and it increased with longer duration of use.

Yan Xie, MPH, of the VA Saint Louis Health Care System and coauthors, wrote that PPIs are linked to a range of serious adverse outcomes – such as acute interstitial nephritis, chronic kidney disease, incident dementia, and *Clostridium difficile* infection – each of which is associated with higher risk of mortality.

"Whether PPI use is associated with excess risk of death is not known and has not been examined in large epidemiological studies spanning a sufficiently long duration of follow-up."

In this study, a cohort of 349,312 veterans initiated on acid-suppression therapy was followed for a mean duration of 5.71 years (BMJ Open 2017. July 4;7:e015735. doi: 10.1136/bmjopen-2016-015735).

Researchers saw a 25% higher risk of death in the 275,977 participants treated

See **PPI** · *page 20*

Health IT: Cybercrime risks are real

Feds offer six-point plan to help.

BY ELI ZIMMERMAN
Frontline Medical News

Aging equipment, valuable data, and an improperly trained workforce make health care IT extraordinarily vulnerable to external malfeasance, as demonstrated by the WannaCry virus episode that occurred this spring in the United Kingdom.

Computer hackers used a weakness in the operating system employed by the U.K. National Health Service, allowing the WannaCry virus to spread quickly across connected systems. The ransomware attack locked clinicians out of patient records and diagnostic machines that were connected, bringing patient care to a near standstill.

The attack lasted 3 days until Marcus Hutchins, a 22-year-old security researcher, stumbled onto a way to slow the spread of the virus enough to manage it, but not before nearly 60 million attacks had been conducted, Salim Neino, CEO of Kryptos Logic, testified June 15 at a joint hearing of two subcommittees of the House Science, Space & Technology Committee. Mr. Hutchins is employed by Kryptos Logic.

U.S. officials are keenly aware that a similar attack could happen here. In June, the federally sponsored Health Care Industry Cybersecurity Task Force issued a report on their year-long

See **Health IT** · *page 39*

Physician burnout common, not readily recognized by sufferers

BY ROXANNE NELSON
Frontline Medical News

AT DDW

CHICAGO – Physician burnout is common, and occurs across specialties including gastroenterology, according to a discussion held at the annual Digestive Disease Week®.

A number of studies and surveys have reported on physician burnout, including a large 2015 report from the Mayo Clinic, which found that 54% of the physicians surveyed had at least one symptom of burnout (Mayo Clin Proc. 2015 Dec;90[12]:1600-13).

Still, physicians often fail to recognize burnout

See **Burnout** · *page 36*

News from DDW2017 Digestive Disease Week® in this issue

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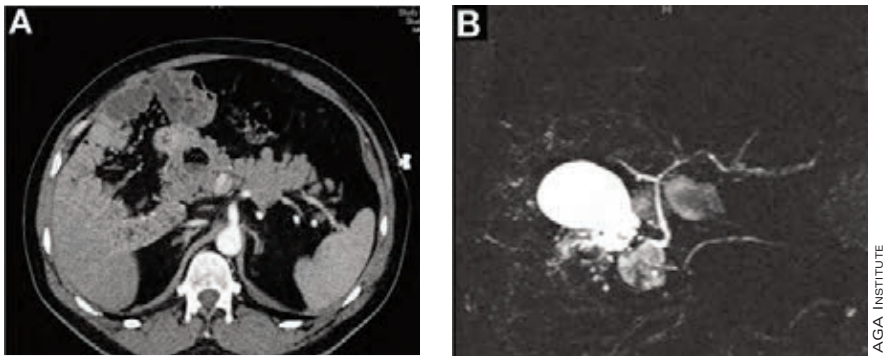
CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

By Crispin Musumba, MBChB, PhD, Edward Britton, MBBS, MRCP, and Howard Smart, MBBS, DM. Published previously in Gastroenterology (2013;144:274, 468-469).

A 50-year-old man presented with a 2-week history of intermittent epigastric pain. His pain typically started 1-2 hours after a meal and lasted for 10 minutes, with associated nausea and vomiting. On the day of admission, the pain had become severe and continuous (lasting 2 hours), exacerbated by lying flat, with accompanying jaundice and rigors. On examination, he was icteric and pyrexial (39.2 °C), with tenderness in the epigastrium and normal bowel sounds. Bloods tests revealed a hemoglobin count of 13.0 g/dL, leukocytosis (13 × 10^9/L), neutrophilia (13.0 × 10^9/L), elevated C-reactive protein (161 mg/L), alanine transaminase (424 U/L), alkaline phosphatase (230 U/L), gamma-glutamyl transpeptidase (579 U/L), bilirubin (77 mmol/L), albumin (32 g/L), glucose (7.4 mmol/L), amylase (375 U/L; normal, less than 150), and a normal lipid profile and calcium levels. Liver ultrasonography was unremarkable.

An abdominal computed tomography (CT) scan was done (Figure A). He was treated conservatively initially with intravenous morphine for pain relief and started on a course of intravenous antibiotics, with good clinical improvement. After improvement of his blood tests, he was discharged a week after admission, and had a magnetic resonance cholangiopancreatography (Figure B) performed as an outpatient. What is the likely diagnosis and pathogenetic mechanisms?



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The diagnosis is on page 26.

LETTER FROM THE EDITOR: Stay alert


DR. ALLEN

This week (July 13, 2017) the U.S. Senate released the next iteration of Repeal and Replace. Most involved in health care delivery oppose Medicaid cuts, relaxation of insurance coverage regulations, making the essential benefit set optional, and other parts of this legislation. And most Americans oppose this legislation, but if I were a hedge-fund manager, I would be shorting the ACA.

On the cover this month you'll read about threats from cybercrime, research questioning the safety of long-term use of proton pump inhibitors (I am going on my 20th year of a PPI), and a story about physician burnout.

This year the AGA journals *Gastroenterology* and *CGH* got extraordinary impact factor scores, with *Gastroenterology* ranked no. 1 for all GI journals. Each month we pull interesting articles from the journals and include summaries. This month, we have stories about autoimmune hepatitis and its relation to HCC, endoscopy's yield for upper GI neoplasms (slow down!), and the impact of heredity in colorectal cancer, among others.

Be sure and read about the new reversal agent for dabigatran (Pradaxa). It turns out that SUNSHINE (vitamin D) may be helpful in metastatic colon cancer. Relatives of NAFLD patients are at increased risk of NAFLD themselves.

From the *Annals of Internal Medicine*, we summarize a large retrospective study again linking interval colon cancers with polypectomy rates of physicians performing screening colonoscopies. The unique twist here is that African American patients tended to be examined by physicians with lower PDRs compared to whites and they had higher interval cancer rates.

We end this month's issue with an article I wrote for *CGH* entitled, "From Obamacare to Trumpcare – implications for gastroenterologists." If you have not guessed, the implications are substantial.

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

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FRONTLINE MEDICAL COMMUNICATIONS

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References: 1. IMS Health, NPA Weekly, May 2017. **2.** Rex DK, DiPalma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. *Gastrointest Endosc.* 2010;72(2):328-336. **3.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2012. **4.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53.

HH13276BT-U

May 2017

Malpractice reform: House passes bill to cap damages

BY ALICIA GALLEGOS
Frontline Medical News

The House of Representatives has passed a bill that would cap damages in medical malpractice cases and impose a tighter time frame for legal challenges against physicians.

The House passed the Protecting Access to Care Act (H.R. 1215) on June 28 by a 218-210 vote. The bill, modeled after California's Medical Injury Compensation Reform Act (MICRA), would limit noneconomic damages in medical malpractice cases to $250,000, restrict contingency fees charged by attorneys, and enforce a 3-year statute of limitations for liability lawsuits from the date of alleged injury. The legislation also includes a fair share rule in which defendants are liable only for the damages in direct proportion to their percentage of responsibility.

The American College of Physicians (ACP) praised the House for passing the bill, saying the time is ripe to develop and pass common-sense liability reforms.

The American Association for Justice, a lobbying organization for plaintiffs' attorneys, sent a letter to the House prior to the bill's passage urging legislators to oppose the bill. More than 75 organizations signed the letter.

The legislation would apply to any patient who receives medical care provided via a federal program, such as Medicare or Medicaid, or via a subsidy or tax benefit, such as coverage purchased under the Affordable Care Act or a replacement. Medical care paid for via employer health plans also would fall under the legislation's umbrella since insurance premiums receive federal tax exemptions. The bill would not preempt state medical malpractice laws that impose damage caps, whether higher or lower than $250,000, nor would the legislation affect the availability of economic damages, according to bill language.

As part of the H.R. 1215, courts could limit how much attorneys receive from a patient's ultimate award. Specifically, courts would have the power to restrict payments from a plaintiff's damage recovery to an attorney who claims a financial stake in the outcome by virtue of a contingent fee.

PIAA, a trade association representing medical liability insurers, said the House passage of the bill is a major victory for tort reform advocates. The bill is the first comprehensive medical liability reform legislation to be passed by either chamber of Congress in more than 5 years, according to PIAA.

"We are now one step closer to enacting federal medical liability reforms that will reduce the nonmeritorious litigation that undermines the physician-patient relationship," Mike Stinson, PIAA vice president of government relations and public policy, said in a statement. "This legislation will truly benefit both patients and healthcare professionals alike."

H.R. 1215 now moves on to the Senate.

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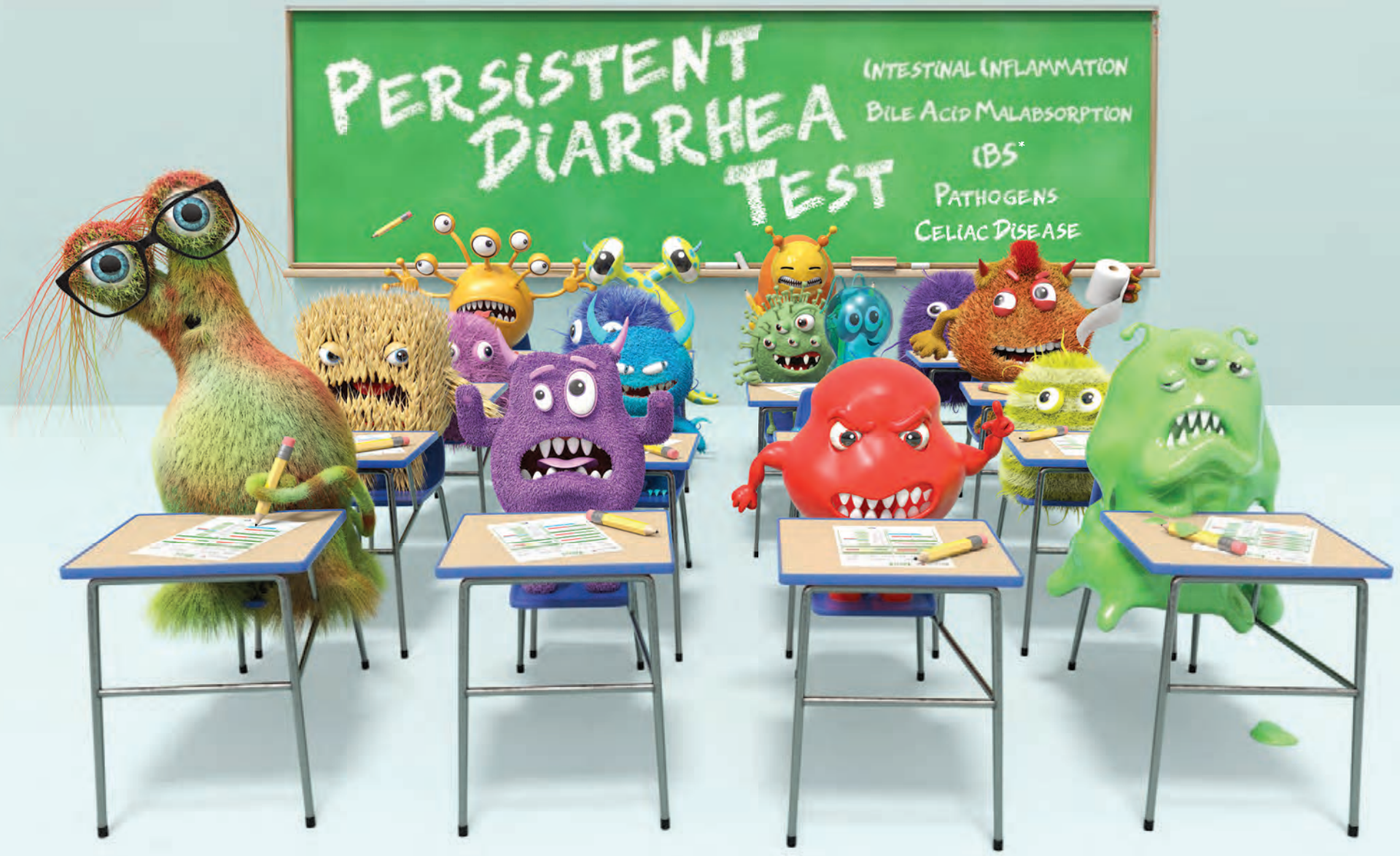

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References: 1. DuPont HL. Persistent diarrhea: a clinical review. *JAMA.* 2016;315(24):2712-2723. **2.** Juckett G, Trivedi R. Evaluation of chronic diarrhea. *Am Fam Physician.* 2011;84(10):1119-1126. **3.** Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol.* 2012;18(42):6036-6059. **4.** Hodges K, Gill R. Infectious diarrhea: cellular and molecular mechanisms. *Gut Microbes.* 2010;1(1):4-21. **5.** Spiller R, Lam C. An update on post-infectious irritable bowel syndrome: role of genetics, immune activation, serotonin and altered microbiome. *J Neurogastroenterol Motil.* 2012;18(3):258-268. **6.** Barkun AN, Love J, Gould M, Pluta H, Steinhart H. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. *Can J Gastroenterol.* 2013;27(11):653-659.

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FLASHBACK TO 2014

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The development of therapies for chronic hepatitis C viral (HCV) infection has been a highlight of progress in hepatology and infectious disease over the last 25 years. From initial empiric approaches with interferon and ribavirin, to targeted and custom designed direct-acting antivirals (DAAs), there has been rapid improvement in efficacy and side effect profiles. Since we are dealing with a viral infection, loss of viremia after stopping therapy (sustained viral response, SVR) has been the marker of therapeutic success. SVR, however, is still a surrogate for clinical outcome and the analysis of 5-year follow-up in the December 2014 issue reported that in patients with SVR there was a reduction in risk of death, hepatocellular carcinoma, and liver transplantation. Three years later, in the age of DAAs, can we say the same? The efficacy of DAAs is very clear with SVR in well over 90% of patients. The clinical trials in DAA's, however, did not monitor mortality as an outcome because the natural history of liver disease from HCV is over many years. For these reasons, and because of the relatively short time that DAAs have been used, quality long-term data do not yet exist to conclusively answer if SVR as a result of DAAs reduces mortality, hepatocellular carcinoma, and liver transplantation.

Observational studies have the potential for significant biases as decisions to treat are frequently based on the likelihood of a successful outcome. A randomized clinical trial for DAAs compared to control would of course be unethical at this stage. The scale of use of DAAs should allow a clear answer to this question within the next 2 years.

Wajahat Mehal, MD, PhD, is a hepatologist, an associate professor of medicine in the department of digestive diseases and hepatology, and the director of the Yale Weight Loss Program, Yale School of Medicine, New Haven, Conn. He is an Associate Editor for GI & Hepatology News.

FROM THE AGA JOURNALS

Autoimmune hepatitis with cirrhosis tied to HCC

BY AMY KARON
Frontline Medical News

The presence of cirrhosis in patients with autoimmune hepatitis markedly increased their risk of hepatocellular carcinoma, according to a systematic review and meta-analysis of 25 cohort studies and 6,528 patients.

Estimated rates of hepatocellular carcinoma (HCC) were 10.1 (95% confidence interval, 6.9-14.7) cases per 1,000 person-years in these patients versus 1.1 (95% CI, 0.6-2.2) cases per 1,000 person-years in patients without cirrhosis at diagnosis, Aylin Tansel, MD, of Baylor College of Medicine in Houston, and associates reported in Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.02.006). Thus, surveillance for HCC "might be cost effective in this population," they wrote. "However, patients with AIH [autoimmune hepatitis] without cirrhosis at index diagnosis, particularly those identified from general populations, are at an extremely low risk of HCC."

Autoimmune hepatitis may be asymptomatic at presentation or may cause severe acute hepatitis or even fulminant liver failure. Even with immunosuppressive therapy, patients progress to cirrhosis at reported annual rates of 0.1%-8%. HCC is the fastest-growing cause of cancer mortality, and the American Association for the Study of Liver Diseases (AASLD) recommends enhanced surveillance for this disease in patients whose annual estimated risk is at least 1.5%. Although the European Association for the Study of Liver Diseases recommends screening for HCC in patients with autoimmune hepatitis and cirrhosis, AASLD makes no such recommendation, the reviewers noted. To study the risk of HCC in patients with autoimmune hepatitis, they searched PubMed, Embase, and reference lists for relevant cohort studies published through June 2016. This work yielded 20 papers and five abstracts with a pooled median follow-up period of 8 years.

The overall pooled incidence of HCC was 3.1 (95% CI, 2.2-4.2) cases per 1,000 person-years, or 1.007% per year, the reviewers wrote. However, the 95% confidence interval for the annual incidence rate nearly encompassed the 1.5% cutoff recommended by AASLD, they said. Furthermore, 5 of 16 studies that investigated the risk of HCC in patients with concurrent cirrhosis reported incidence rates above 1.5%. Among 93 patients who developed HCC in the meta-analysis, only 1 did not have cirrhosis by the time autoimmune hepatitis was diagnosed.

The meta-analysis also linked HCC to older age and Asian ethnicity among patients with autoimmune hepatitis, as

Continued on following page

Serial imaging surveillance facilitates detection of hepatocellular carcinoma (HCC) at a stage amenable to potentially curative resection or liver transplantation. The AASLD, EASL, and APASL recommend surveillance for cirrhotic patients; however, the AASLD stipulates that the incidence of HCC exceed the threshold of cost-effectiveness of 1.5% per year. Whether HCC surveillance in cirrhotic patients with autoimmune hepatitis (AIH) is cost effective remains controversial. The systematic review and meta-analysis by Tansel et al. of 25 rigorously selected cohort studies of AIH addresses this question by calculating incidence rates of HCC per 1,000 person-years using 95% confidence intervals derived from event rates in relation to the duration of follow-up. As expected, the incidence rate of HCC was significantly increased in cirrhotic AIH patients: 10.07 (95% CI, 6.89-14.70) cases per 1,000 patient-years. In contrast, the incidence rate was insignificant in noncirrhotic patients: 1.14 (95% CI, 0.60-2.17) cases per 1,000 patient-years. The pooled incidence of HCC in cirrhotic AIH patients was 1.007% per year. However, the 95% CI nearly encompassed the threshold of 1.5%, and in 5 of the 16 studies incidence rates exceeded 1.5% per year. Multivariate analysis identified older age, male sex, cirrhosis status at baseline, number of AIH relapses, and alcohol use as independent risk factors for HCC. This study supports the 2015 recommendation of EASL to perform HCC surveillance in cirrhotic patients with AIH. In addition, it underscores the deleterious effects of multiple attempts to withdraw immunosuppression and alcohol use, which should be avoided.

John M. Vierling, MD, FACP, FAASLD, is professor of medicine and surgery, chief of hepatology, Baylor College of Medicine, Houston. He has received grant support from Taiwan J and Novartis and is on the scientific advisory board for Novartis.

FROM THE AGA JOURNALS

Anticoagulation OK for cirrhosis patients with PVT

BY AMY KARON
Frontline Medical News

Patients with cirrhosis and portal vein thrombosis (PVT) who received anticoagulation therapy had nearly fivefold greater odds of recanalization compared with untreated patients, and were no more likely to experience major or minor bleeding, in a pooled analysis of eight studies published in the August issue of Gastroenterology (doi: 10.1053/j.gastro.2017.04.042).

Rates of any recanalization were 71% in treated patients and 42% in untreated patients (*P* less than .0001), wrote Lorenzo Loffredo, MD, of Sapienza University, Rome, and his coinvestigators. Rates of complete recanalization were 53% and 33%, respectively (*P* = .002), rates of spontaneous variceal bleeding were 2% and 12% (*P* = .04), and bleeding affected 11% of patients in each group. Together, the findings "show that anticoagulants are efficacious and safe for treatment of portal vein thrombosis in cirrhotic patients," although larger, interventional clinical trials are needed to pinpoint the clinical role of anticoagulation in cirrhotic patients with PVT, the reviewers reported.

PVT affects about 20% of patients and predicts poor outcomes, they noted. Although some studies support anticoagulating these patients, data are limited. Therefore, the reviewers searched PubMed, the ISI Web of Science, SCOPUS, and the Cochrane database through Feb. 14, 2017, for trials comparing anticoagulation with no treatment in patients with cirrhosis and PVT.

This search yielded eight trials of 353 patients who received low-molecular-weight heparin, warfarin, or no treatment for about 6 months, with a typical follow-up period of 2 years. The reviewers found no evidence of publication bias or significant heterogeneity among the trials. Studies evaluated complete recanalization, progression of PVT, major or minor bleeding events, and spontaneous variceal bleeding. Compared with no treatment, anticoagulation was tied to a significantly greater likelihood of complete recanalization (pooled odds ratio, 3.4; 95% confidence interval, 1.5-7.4; *P* = .002), a significantly lower chance of PVT progressing (9% vs. 33%; pooled OR, 0.14; 95% CI, 0.06-0.31; *P* less than .0001), no difference in bleeding rates (11% in each pooled group), and a significantly lower risk of spontaneous variceal bleeding (OR, 0.23; 95% CI, 0.06-0.94; *P* = .04).

"Low-molecular-weight heparin, but not warfarin, was significantly associated with a complete PVT resolution as compared to untreated patients, while both low-molecular-weight heparin and warfarin were effective in reducing PVT progression." That finding merits careful interpretation, however, because most studies on warfarin were retrospective and lacked data on the quality of anticoagulation, they added.

"It is a challenge to treat patients with cirrhosis using anticoagulants because of the perception that the coexistent coagulopathy could promote bleeding," the researchers wrote. Nonetheless, their analysis suggests that anticoagulation has significant benefits and does not increase bleeding risk, regardless of the severity of liver failure, they concluded.

The reviewers reported having no funding sources or conflicts of interest.

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Obeticholic acid doesn't prevent liver damage in pigs

BY HEIDI SPLETE
Frontline Medical News

Obeticholic acid (OCA) failed to prevent the development of short-bowel syndrome–associated liver disease (SBS-ALD) in a preliminary study using piglet models. The findings were published in the July issue of Cellular and Molecular Gastroenterology and Hepatology (doi: 10.1016/j.jcmgh.2017.02.008).

Current treatment options for SBS-ALD, wrote Prue M. Pereira-Fantini, PhD, of Murdoch Childrens Research Institute, Victoria, Australia, and colleagues. However, the farnesoid X receptor, which regulates genes involved in bile acid synthesis, absorption, and transport in the intestine and liver, has shown promise as a pharmaceutical target.

"Recently, we described SBS-ALD-associated alterations in bile acid composition associated with disrupted farnesoid X receptor (FXR) signaling mechanisms," the researchers said. OCA has been shown to prevent liver disease in mouse models and human disease, and the researchers explored whether it would be effective in the context of SBS-ALD.

The researchers randomized piglets into four groups to receive small-bowel resection or sham surgery, and either a daily dose of 2.4 OCA mg/kg per day or no treatment. The pigs were euthanized 2 weeks after their surgeries, and the researchers collected portal plasma bile, and liver samples.

OCA treatment in piglets in the SBS surgery group was associated with decreased stool fat that suggested improved fat absorption, but impacted liver morphology, the researchers noted. "Untreated, sham-operated piglets showed normal liver histology when compared with SBS piglets who showed decreased hepatic lobule area and small clusters of inflammatory cells together with mild-to-moderate vesicular zone 2 lipidosis," they wrote.

Overall, OCA treatment prevented the depletion of taurine; taurine concentration was approximately 8 ng/mL for SBS piglets with treated with OCA compared with 8 ng/mL in the sham group, 9 ng/mL in the sham plus OCA group, and 3 ng/mL in the SBS-only group. However, bile acid dysmetabolism occurred as shown by hyodeoxycholic acid levels, which increased with OCA treatment compared to sham controls but were significantly reduced in SBS piglets treated with OCA vs. untreated SBS piglets.

In addition, the researchers found that small-bowel resection did not impact gene expression levels of FXR targets in the intestine or liver. However, "intestinal FXR gene expression was 11-fold higher in untreated SBS piglets when compared with untreated sham piglets," they wrote. OCA treatment had no significant impact on FXR gene expression in the OCA-treated group vs. the untreated group and in the OCA-treated SBS group.

The findings were limited by use of an animal model, but the results suggest that OCA treatment may have clinical benefits for SBS patients by reducing fat malabsorption, the researchers wrote. However, OCA "did not prevent the development of SBS-ALD, thereby limiting the potential therapeutic benefit in patients with SBS," they concluded.

The researchers had no financial conflicts to disclose. The study was supported in part by the National Health and Medical Research Council of Australia and by a research grant from the Science Foundation Ireland.

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Continued from previous page

has been reported before. Male sex only slightly increased the risk of HCC, but the studies included only about 1,130 men, the reviewers noted. Although the severity of autoimmune hepatitis varied among studies, higher rates of relapse predicted HCC in two cohorts. Additionally, one study linked alcohol abuse to a sixfold higher risk of HCC among patients with autoimmune hepatitis. "These data support careful monitoring of patients with autoimmune hepatitis, particularly older men, patients with multiple autoimmune hepatitis relapses, and those with ongoing alcohol abuse," the investigators wrote.

They found no evidence of publication bias, but each individual study included at most 15 cases of HCC, so pooled incidence rates were probably imprecise, especially for subgroups, they said. Studies also inconsistently reported HCC risk factors, often lacked comparison groups, and usually did not report the effects of surveillance for HCC.

Dr. Tansel reported receiving support from the National Institutes of Health. The reviewers had no conflicts of interest.

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FROM THE AGA JOURNALS

Endoscopists who took longer found more neoplasms

BY AMY KARON
Frontline Medical News

Endoscopists who took about a minute longer during screening esophagogastroduodenoscopy (EGD) detected significantly more upper gastrointestinal neoplasms than their quicker colleagues, in a retrospective study reported in the August issue of Gastroenterology (doi: 10.1053/j.gastro.2017.05.009).

Detection rates were 0.28% and 0.20%, respectively (P = .005), and this difference remained statistically significant after the investigators controlled for numerous factors that also can affect the chances of detecting gastric neoplasms during upper endoscopy, reported Jae Myung Park, MD, and his colleagues at Seoul (South Korea) St. Mary's Hospital.

Gastric cancer is the second leading cause of cancer mortality worldwide, they noted. Although EGD has been practiced globally for decades, there is no consensus on which performance metrics optimize diagnostic yield. Both South Korea and Japan have adopted screening EGD to help diagnose gastric cancer, but interval cancers and false-positive results remain concerns, and the field lacks rigorous analyses comparing EGD time with gastric cancer detection rates. Therefore, the researchers studied 111,962 consecutive patients who underwent EGD at one hospital in Seoul from 2009 through 2015. Fourteen board-certified endoscopists performed these procedures at a single endoscopy unit.

A total of 262 patients (0.23%) were diagnosed with gastric neoplasia or dysplasia, duodenal neoplasia, or esophageal carcinoma. This finding closely resembled a prior report from Korea, the investigators noted. Detection rates among individual endoscopists ranged from 0.14% to 0.32%, and longer EGD time was associated with a higher detection rate with an R value of 0.54 (P = .046). During the first year of the study, EGDs without biopsies averaged 2 minutes and 53 seconds. Based on this finding, the researchers set a cutoff time of 3 minutes and classified eight endoscopists as fast (mean EGD duration, 2 minutes and 38 seconds; standard deviation, 21 seconds) and six endoscopists as slow (mean duration, 3 minutes and 25 seconds; SD, 19 seconds).

Slower endoscopists were significantly more likely to detect gastric adenomas or carcinomas, even after the investigators controlled for the biopsy rates and experience level of these endoscopists and patients' age, sex, smoking status, alcohol use, and family history of cancer (odds ratio, 1.52; 95% confidence interval, 1.17-1.97; P = .0018).

Older age, male sex, and smoking also were significant correlates of cancer detection in the multivariable model. Biopsy rates among endoscopists ranged from 7% to 28%, and taking a biopsy was an even stronger predictor of detecting an upper GI neoplasm than was EGD duration, with an R value of 0.76 (P = .002). Although this study was observational and retrospective and lacked data on prior EGD examinations, surveillance intervals, and rates of false-negative results, it "supports the hypothesis that examination duration affects the diagnostic accuracy of EGD," Dr. Park and his coinvestigators reported. "Prolonging the examination time will allow more careful examination by the endoscopist, which will enable the detection of more subtle lesions. Based on our data, we believe that these indicators can improve the quality of EGD."

Funders included the Ministry of Education, Science, and Technology; the Ministry of Science, ICT, and Future Planning; and the Ministry of Health & Welfare, Republic of Korea. The investigators reported having no conflicts of interest.

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Screening and surveillance practices remain one of the major indications for performing upper endoscopy in patients to detect esophageal (adenocarcinoma in the West; squamous cell in the East) and gastric cancer (in the East). The goal of the initial endoscopy is to detect precancerous lesions (such as Barrett's esophagus and gastric intestinal metaplasia) and, if detected, to grade them properly and evaluate for the presence of dysplasia and cancer in subsequent surveillance examinations.


DR. SHARMA

The primary aim of the retrospective study by Park et al. was to determine the association between the duration of upper endoscopy and the rate of upper GI neoplasia cases detected during the procedure. Endoscopists spending more than 3 minutes were more likely to diagnose lesions during esophagogastroduodenoscopy than were those who spent less time during the procedure. While the study has limitations, including its retrospective nature, the performance of an adequate number of biopsies, and the type of endoscopes utilized, it does highlight a more important issue – the role of quality endoscopy for the detection of upper GI neoplasia. Besides the time spent during upper endoscopy (like the colonoscopy withdrawal time), other considerations during index endoscopy, to ensure a quality examination, are careful inspection of the mucosa and detection of lesions during endoscopy. A high-quality examination of the esophageal mucosa can lead to an increase in detection of dysplasia and cancer in patients with Barrett's esophagus. A recent study determined that, when endoscopists spent approximately a minute per centimeter extent of Barrett's esophagus, they had a higher detection rate of neoplastic lesions. Such a "quality examination" could be easily implemented and should be the minimal standard in surveillance of patients with Barrett's esophagus. In summary, after the initial attention to quality colonoscopy, we are now in the process of moving to assessing quality in upper endoscopy. Details of endoscopic techniques and duration of endoscopic examination are the first steps. In a specialty driven by evidence-based guidelines, quality indicators become most important to ensure appropriate diagnosis, surveillance, and treatment.

Prateek Sharma, MD, is a professor of medicine in the division of gastroenterology and hepatology, Veterans Affairs Medical Center, University of Kansas, Kansas City, Mo. He has no conflicts of interest.

Heritability of colorectal cancer estimated at 40%

BY AMY KARON
Frontline Medical News

Genetic factors accounted for about 40% of variability in the risk of colorectal cancer (CRC) in an analysis of monozygotic and same-sex dizygotic twins from the Nordic Twin Study of Cancer reported in the August issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.12.041).

Thus, CRC "has a substantial heritable component, and may be more heritable in women than men," Rebecca E. Graff, ScD, of the Harvard T.H. Chan School of Public Health, Boston, and the University of California, San Francisco, and her colleagues wrote. "Siblings, and particularly monozygotic cotwins, of individuals with colon or rectal cancer should consider personalized screening," they added.

Having a first-degree relative with CRC doubles to triples the risk of this disease, the researchers noted. About one in five CRC patients has an affected relative, but less than 10% of inheritance is autosomal dominant, and common risk loci explain only about 8% of CRC heritability. Genomewide association studies have identified more than 50 susceptibility variants for CRC, but these explain only 1%-4% of genetic variation in CRC. Previous studies of twins found that 9%-35% of these cancers were heritable, but Dr. Graff and her associates obtained estimates of about 15% after accounting for censoring and competing risk of

Continued on following page

Task Force's updated recommendations for CRC screening

The U.S. Multi-Society Task Force on Colorectal Cancer has updated their recommendations for screening in average-risk individuals beginning at age 50, which they have long endorsed. The new recommendations, "Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer," were published in the July issue of Gastroenterology (2017;112[7]:1016-1030).

Screening tests

The task force ranked screening tests in three tiers based on performance features, costs, and practical considerations.

First-tier tests

Colonoscopy every 10 years and annual fecal immunochemical test (FIT) are recommended as the cornerstones of screening regardless of how screening is offered. Patients should first be offered colonoscopy, followed by FIT for patients who decline colonoscopy. Colonoscopy and FIT should be recommended as tests of choice when multiple options are presented as alternatives. It is appropriate to use colonoscopy screening in high-prevalence populations and FIT screening in populations with an estimated low prevalence of advanced neoplasia, as well as in organized screening programs.

Second-tier tests

These tests are appropriate screenings, but each has disadvantages relative to the tier-one tests:

- CT colonography every 5 years.
- FIT–fecal DNA test every 3 years.
- Flexible sigmoidoscopy every 5-10 years.

Third-tier test

- Capsule colonoscopy every 5 years is recommended as a third-tier test because of limited evidence and current obstacles to use.

The task force suggests that the Septin9 serum assay (Epigenomics, Seattle) not be used for screening.

Other considerations

The task force notes that there are considerations to be taken into account with individuals who are not at average risk.

- Persons with a history of CRC or a documented advanced adenoma in a first-degree relative under age 60 or two first-degree relatives with these findings at any age are recommended to undergo screening by colonoscopy every 5 years, beginning 10 years before the age at diagnosis of the youngest affected relative, or at age 40, whichever is earlier.
- Persons with a single first-degree relative diagnosed at aged 60 or over with CRC or an advanced adenoma can be offered average-risk screening options beginning at age 40.
- African American patients should be screened beginning at age 45.
- Adults age younger than 50 years with colorectal bleeding symptoms should undergo colonoscopy or an evaluation sufficient to determine a bleeding cause, initiate treatment, and complete follow-up to determine resolution of bleeding.
- Persons who are up to date with screening and have negative prior screening tests, particularly colonoscopy, can consider stopping screening at age 75 or when life expectancy is less than 10 years.
- Persons without prior screening should be considered for screening up to age 85, depending on consideration of their age and comorbidities.

The U.S. Multi-Society Task Force of Colorectal Cancer is a panel of expert gastroenterologists representing the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy.

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Continued from previous page

death. To better pinpoint CRC heritability by sex and age, the investigators compiled data from 39,990 monozygotic and 61,443 same-sex dizygotic twins from the Nordic Twin Study of Cancer, which included population-based twin registries from Denmark, Finland, Norway, and Sweden.

Between 1943 and 2010, a total of 1,861 participants were diagnosed with colon cancer and 1,268 were diagnosed with rectal cancer. If a monozygotic twin developed CRC, his or her twin had about a threefold higher risk of CRC than did the overall cohort (familial risk ratio, 3.1; 95% confidence interval, 2.4-3.8). If a dizygotic twin developed CRC, the same-sex twin had about twice the risk of that of the rest of the cohort (FRR, 2.2; 95% CI, 1.7-2.7). For both monozygotic and same-sex dizygotic twins, the familial risk ratios for colon cancer and rectal cancer were slightly higher (3.3 and 2.6, respectively) than for CRC overall. "These differences could reflect limited power but also could indicate shared genetic factors contributing to both [cancer] sites," the researchers wrote.

The model that best fits the data accounted for additive genetic and environmental effects, the researchers said. Based on this model, genetic factors explained about 40% (95% CI, 33%-48%) of variation in the risk of CRC. Thus, the heritability of CRC was about 40%. The estimated heritability of colon cancer was 16% and that of rectal cancer was 15%, but confidence intervals were wide, ranging from 0% to 47% or 50%, respectively. Individual environmental factors accounted for most of the remaining risk of colon and rectal cancers.

Funders included the Ellison Foundation, the Odense University Hospital AgeCare program, the Academy of Finland, US BioSHaRE-EU, the European Union's Seventh Framework Programme, BioSHaRE-EU, the Swedish Ministry for Higher Education, the Karolinska Institutet, and the National Cancer Institute. Dr. Graff had no conflicts of interest.

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DDSEP eight
Digestive Diseases Self-Education Program

Quick Quiz

Q1: A 64-year-old man arrives at the transplant clinic for his annual post-transplant assessment. He received a deceased-donor liver transplant 4 years ago for nonalcoholic steatohepatitis (NASH)–related cirrhosis. His immediate postoperative course was unremarkable, but he does have posttransplant hypertension, diabetes mellitus (diet controlled), and obesity. His alanine aminotransferase and aspartate aminotransferase levels have been modestly elevated at 1-3 times the upper limit of normal for 2.5 years.

Multiple liver biopsies have shown only nonspecific inflammation, with no features of cellular- or antibody-mediated rejection, or recurrent NASH. Medications include tacrolimus, mycophenolate mofetil, amlodipine, and low-dose aspirin. Tacrolimus trough levels have ranged from 8 to 10 ng/mL intentionally as it was thought that the liver test abnormalities may be an immunologically driven phenomenon despite the lack of objective liver biopsy–based evidence. As a new provider for this patient, you decide to recheck several laboratory values to rule out alternative reasons for the elevated aminotransferases. The lab results are as follows: hepatitis B DNA negative, hepatitis C RNA negative, smooth muscle antibody negative, anti-nuclear antibody negative, pANCA negative, hepatitis E IgG positive.

What is the best treatment for this patient?
A. Observation
B. Ribavirin
C. Sofosbuvir
D. Pegylated interferon

Q2: A 10-year-old boy is referred after he was noted to have lost weight over the past year during a routine physical exam. He denies trying to lose weight. He has occasional abdominal pain and intermittent watery nonbloody diarrhea, which do not seem associated with particular foods. He also complains of feeling bloated and his mother reports that "his belly always looks swollen." He has had no other symptoms of illness. On physical exam, he is slender and has a mildly distended and tympanitic abdomen.

Which of the following is the next best step in the evaluation?
A. Lactose breath test
B. *H. pylori* serology
C. Immediate esophagogastroduodenoscopy (EGD) and colonoscopy
D. Blood for CBC, serum iron, and anti-tissue transglutaminase antibodies
E. Stool for ova and parasites

The answers are on page 30.

DDW named session opportunities

As part of the AGA Research Foundation's efforts to raise funds to support young researchers in gastroenterology and hepatology, a program has been established to provide donor recognition for AGA Institute Council sessions at Digestive Disease Week®.

There are currently five named sessions in this program honoring Farron and Martin Brotman, Michael and Josephine Camilleri, Donald O. Castell, Kiron and Kamala Das, and Kristin and David Peura.

"I have dedicated my career to the care and research of patients with ulcerative colitis and Crohn's disease," remarked Kiron Das, MD, PhD, AGAF, "and we are so happy to have the ability to support the AGA and its important missions in research and education."

Individuals interested in receiving name recognition for an AGA Institute Council session at DDW can do so by contributing an unrestricted gift of $125,000 or more, payable over 5 years, to the AGA Research Foundation. Naming rights are offered for 10 years. Donors can specify a particular AGA Institute Council section, if so desired, and one of the lectures sponsored by that section will bear his/her name.

"Our support is intended to give back to the AGA and to our specialty in appreciation of all the benefits in education, practice, and research that I received over the past 33 years as an attendee of AGA meetings and as a beneficiary of the AGA/SmithKline Beecham Clinical Research Award in 1988," said Michael Camilleri, MD, AGAF. "It's also an expression of gratitude for the opportunity to serve the AGA and the specialty of gastroenterology in many different ways."

"As a practicing academic clinical gastroenterologist, I have personally benefitted from attending and participating in research symposia over the four decades that I have been an AGA member," stated David A. Peura, MD, AGAF. "It was an easy decision for my wife Kristin and I to provide philanthropic support to ensure this forum remains viable and vital for future generations of practicing digestive disease specialists."

The AGA Research Foundation supports young researchers who are conducting novel research and coming up with new ideas to advance the science and practice of gastroenterology and hepatology. Donations to the foundation are an investment in the next generation of GI investigators.

"I have been dedicated to supporting research in gastroenterology throughout my career," said Martin Brotman, MD, AGAF. "As a clinical practitioner, I have benefitted daily – as have my patients – from the knowledge developed and disseminated by basic, translational, and clinical researchers. Farron and I were pleased to have the opportunity to give back by making a gift to the AGA Research Foundation to support its vitally important programs that fund investigators at a critical time in their careers. We are honored to have our names associated with a state-of-the-art education symposium in an area of gastroenterology that was a major interest of mine throughout my years in practice. The new knowledge to be presented in this symposium is testimony to the importance of research funding."

If you are interested in learning more about named sessions and/or seeking support to solicit donations from others in your name, please contact Stacey Tuneski, Senior Director of Development and Foundation Programs, at stuneski@gastro.org or 301-222-4005.

The AGA Research Foundation raises funds to support young researchers. For more information or to make a contribution, visit www.gastro.org/foundation.

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Get involved with AGA

We're soliciting members to serve in AGA leadership positions – as committee and center members, as well as on the AGA Institute Governing Board. This is an opportunity to network with other physicians and scientists, pursue a special interest, and make an impact in an area that is important to you.

Join a committee or center

AGA and AGA Institute are seeking members to serve on several committees and centers that recommend and oversee new and existing policies and programs. Terms will start in June 2018; nominations must be received by Nov. 1, 2017. Members can either nominate themselves or other members. For more information on the positions available, take a look at the AGA Committee page, http://www.gastro.org/about/people/committees.

Serve in a leadership position

The AGA Nominating Committee is in the midst of identifying candidates to join the governing board – in the offices of vice president, clinical research councillor, and practice councillor – as well as 10 nominees for the 2018-2019 AGA Nominating Committee. To learn more, or to nominate yourself or a colleague, email dfield@gastro.org. Nominations are due by Oct. 1, 2017; earlier submissions are encouraged.

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Mark your calendar: 2018 AGA grants cycle announced

The AGA Research Foundation is excited to announce the start of its 2018 Research Grants cycle. This year the foundation will be awarding over $2 million in funding to support researchers within gastroenterology and hepatology. Now is your chance to view upcoming opportunities and plan your applications. Learn more below about the first application due in August, and visit the AGA Research Funding website (www.gastro.org/research-funding) for the full list. Contact awards@gastro.org with any questions.

Applications due: Aug. 4, 2017
AGA-R. Robert & Sally Funderburg Research Award in Gastric Cancer

This award provides $50,000 per year for 2 years to an established investigator working on novel approaches in gastric cancer research. For the past 25 years, this $100,000 award has enhanced the fundamental understanding of gastric cancer pathobiology toward ultimately developing a cure for the disease.

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Crohn's & Colitis Congress registration open

Join the Crohn's & Colitis Foundation and AGA for the inaugural Crohn's & Colitis Congress™. Expand your knowledge, network with inflammatory bowel diseases (IBD) leaders across multiple disciplines and get inspired to improve patient care.

The Crohn's & Colitis Congress, taking place Jan. 18-20, 2018, in Las Vegas, combines the strengths of the nation's leading IBD patient organization, Crohn's & Colitis Foundation, and the premier GI professional association, AGA. Together we are committed to convening the greatest minds in IBD to transform patient care and accelerate the pace of research.

The Crohn's & Colitis Congress offers a bold multidisciplinary, clinically focused and forward-thinking program. The organizing committee and faculty represent key disciplines involved in the comprehensive care of IBD patients, as well as the foremost minds in research.

Sessions will emphasize case studies with multidisciplinary panel discussions covering:

- Management of complicated IBD
- Defining optimal treatment algorithms
- Clinical and research challenges

Take a critical step toward finding cures and improving the lives of adults and children living with IBD. Learn more about the congress and register today by visiting www.crohnscolitiscongress.org.

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GI & HEPATOLOGY NEWS

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Possible risk may restrict usage

PPI *from page 1*

with PPIs, compared with that in those who were treated with H_2-receptor antagonists (95% confidence interval, 1.23-1.28), after adjusting for factors such as estimated glomerular filtration rate, age, hospitalizations, and a range of comorbidities, including gastrointestinal disorders.

When PPI use was compared with no PPI use, there was a 15% increase in the risk of death (95% CI, 1.14-1.15). When compared with no known exposure to any acid suppression therapy, the increased risk of death was 23% (95% CI, 1.22-1.24).

In an attempt to look at the risk of death in a lower-risk cohort, the researchers analyzed a subgroup of participants who did not have the conditions for which PPIs are normally prescribed, such as gastroesophageal reflux disease, upper gastrointestinal tract bleeding, ulcer disease, *Helicobacter pylori* infection, and Barrett's esophagus.

However, even in this lower-risk cohort, the study still showed a 24% increase in the risk of death with PPIs, compared with that in H_2-receptor antagonists (95% CI, 1.21-1.27); a 19% increase with PPIs, compared with no PPIs; and a 22% increase with PPIs, compared with no acid suppression.

Duration of exposure to PPIs was also associated with increasing risk of death. Participants who had taken PPIs for fewer than 90 days in total had only a 5% increase in risk, while those taking them for 361-720 days had a 51% increased risk of death.

"Although our results should not deter prescription and use of PPIs where medically indicated, they may be used to encourage and promote pharmacovigilance and emphasize the need to exercise judicious use of PPIs and limit use and duration of therapy to instances where there is a clear medical indication and where benefit outweighs potential risk," the authors wrote.

"Standardized guidelines for initiating PPI prescription may lead to reduced overuse [and] regular review of prescription and over-the-counter medications, and deprescription, where a medical indication for PPI treatment ceases to exist, may be a meritorious approach."

Examining possible physiologic mechanisms to explain the increased risk of death, the authors noted that animal studies suggested PPIs may limit the liver's capacity to regenerate.

PPIs are also associated with increased activity of the heme oxygenase-1 enzyme in gastric and endothelial cells and impairment of lysosomal acidification and proteostasis and may alter gene expression in the cellular retinol metabolism pathway and the complement and coagulation cascades pathway.

However, the clinical mediator of the heightened risk of death was likely one of the adverse events linked to PPI use, they said.

The authors declared no relevant financial conflicts of interest.

'Although our results should not deter prescription and use of PPIs where medically indicated, they may be used to encourage and promote pharmacovigilance and emphasize the need to exercise judicious use of PPIs and limit use and duration of therapy.'

Review AGA's "Guide to Conversations About the Latest PPI Research Results" for tips on talking with your patients about this research study at http://www.gastro.org/news_items/a-guide-to-conversations-about-the-latest-ppi-research-results.

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Idarucizumab reversed dabigatran completely and rapidly

BY AMY KARON
Frontline Medical News

One IV 5-g dose of idarucizumab completely, rapidly, and safely reversed the anticoagulant effect of dabigatran, according to final results for 503 patients in the multicenter, prospective, open-label, uncontrolled RE-VERSE AD study.

Uncontrolled bleeding stopped a median of 2.5 hours after 134 patients received idarucizumab. In a separate group of 202 patients, 197 were able to undergo urgent procedures after a median of 1.6 hours, Charles V. Pollack, MD, and his associates reported at the International Society on Thrombosis and Haemostasis congress. The report was simultaneously published in the New England Journal of Medicine.

The study uncovered no serious safety signals, and rates of thrombosis were 4.8% and 6.8% at 30 and 90 days, respectively, which resembled other reports of these patient populations (N Engl J Med. 2017 Jul 11. doi: 10.1056/NEJMoa1707278).

Idarucizumab was specifically developed to reverse the anticoagulant effect of dabigatran. Many countries have already licensed the humanized monoclonal antibody fragment based on interim results for the first 90 patients enrolled in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study (NCT02104947), noted Dr. Pollack, of Thomas Jefferson University, Philadelphia.

The final RE-VERSE AD cohort included 301 patients with uncontrolled gastrointestinal, intracranial, or trauma-related bleeding and 202 patients who needed urgent procedures. Participants from both groups typically were white,

Courtesy International Society on Thrombosis and Haemostasis

Dr. Charles V. Pollack presented findings on idarucizumab at the ISTH congress.

in their late 70s (age range, 21-96 years), and receiving 110 mg (75-150 mg) dabigatran twice daily. The primary endpoint was maximum percentage reversal within 4 hours after patients received idarucizumab, based on diluted thrombin time and ecarin clotting time.

The median maximum percentage reversal of dabigatran was 100% (95% confidence interval, 100%-100%) in more than 98% of patients, and the effect usually lasted 24 hours. Among patients who underwent procedures, intraprocedural hemostasis was considered normal in 93% of cases, mildly abnormal in 5% of cases, and moderately abnormal in 2% of cases, the researchers noted. Seven patients received another dose of idarucizumab after developing recurrent or postoperative bleeding.

A total of 24 patients had an adjudicated thrombotic event within 30 days after receiving idarucizumab. These events included pulmonary embolism, systemic embolism, ischemic stroke, deep vein thrombosis, and myocardial infarction. The fact that many patients did not restart anticoagulation could have contributed to these thrombotic events, the researchers asserted. They noted that idarucizumab had no procoagulant activity in studies of animals and healthy human volunteers.

About 19% of patients in both groups died within 90 days. "Patients enrolled in this study were elderly, had numerous coexisting conditions, and presented with serious index events, such as intracranial hemorrhage, multiple trauma, sepsis, acute abdomen, or open fracture," the investigators wrote. "Most of the deaths that occurred within 5 days after enrollment appeared to be related to the severity of the index event or to coexisting conditions, such as respiratory failure or multiple organ failure, whereas deaths that occurred after 30 days were more likely to be independent events or related to coexisting conditions."

Boehringer Ingelheim Pharmaceuticals provided funding. Dr. Pollack disclosed grant support from Boehringer Ingelheim during the course of the study and ties to Daiichi Sankyo, Portola, CSL Behring, Bristol-Myers Squibb/Pfizer, Janssen Pharma, and AstraZeneca. Eighteen coinvestigators also disclosed ties to Boehringer Ingelheim and a number of other pharmaceutical companies. Two coinvestigators had no relevant financial disclosures.

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SUNSHINE: High-dose vitamin D boosts progression-free survival in metastatic CRC

BY SUSAN LONDON
Frontline Medical News

CHICAGO – High-dose vitamin D supplementation is a simple, safe approach for improving on the efficacy of first-line chemotherapy for metastatic colorectal cancer, suggest findings of the SUNSHINE trial reported at the annual meeting of the American Society of Clinical Oncology.

"Vitamin D has shown anti-neoplastic properties in the laboratory, including inhibition of cell proliferation and angiogenesis, induction of cell differentiation and apoptosis, as well as anti-inflammatory and immunomodulatory effects," said lead author Kimmie Ng, MD, director of clinical research and a Gastrointestinal Cancer Center physician at the Dana-Farber Cancer Institute in Boston.

"The vitamin D hypothesis is also supported by a large body of epidemiologic evidence, both from our group as well as from others, that have shown that higher plasma 25-hydroxyvitamin D levels are associated with improved survival in patients with colorectal cancer," she added.

Notably, in the CALGB/SWOG 80405 trial of first-line therapy for colorectal cancer, patients' median 25-hydroxyvitamin D level at baseline fell below the cutoff for deficiency (ASCO 2015 meeting, Abstract 3503). Moreover, those having higher levels ultimately had better overall survival even after other factors were taken into account.

In the SUNSHINE trial, the investigators studied 139 patients with untreated metastatic colorectal cancer. Results showed that those given FOLFOX chemotherapy and the antiangiogenic agent bevacizumab (Avastin) plus high-dose vitamin D had a one-third lower risk of progression or death compared with counterparts given the same regimen plus low-dose vitamin D.

High-dose supplementation was not associated with greater toxicity. In fact, patients in that group had a much lower incidence of grade 3 or 4 diarrhea.

"After a decade of observational data linking higher vitamin D status with improved outcomes in colorectal cancer patients, SUNSHINE is the first completed randomized double-blind controlled clinical trial of vitamin D supplementation for treatment of colorectal cancer," Dr. Ng said. "The trial met its primary endpoint. Given this data, a larger, confirmatory phase III trial is warranted."

"The vitamin D hypothesis is also supported by a large body of epidemiologic evidence."

DR. NG

The investigators are performing subgroup analyses and analyzing overall survival, and will measure patients' 25-hydroxyvitamin D levels in plasma samples collected serially throughout the study to determine whether they correlate with outcomes.

In addition, "to help understand and elucidate underlying mechanisms and biology, we have planned several correlative studies looking at tumoral and plasma biomarkers related to the vitamin D pathway, inflammation, and tumor immunity, among other pathways," she further noted. "We will also be conducting next-generation sequencing and gene expression analyses."

Expert perspective

"It will be interesting to know [patients' vitamin D levels] as the majority of patients were enrolled in New England, where I think there is a little less sunshine than in other parts of the United States, so perhaps the vitamin D levels will reflect that," said invited discussant Andrea Cercek, MD, of Memorial Sloan Kettering Cancer Center in New York.

Data on vitamin D pertaining to chemoprevention and to outcomes in other malignancies have been mixed, she cautioned. For example, supplementation did not reduce the risk of recurrent colorectal adenomas in one study (N Engl J Med. 2015;373:1519-30), and benefit or harm in terms of developing advanced colorectal adenomas in another study hinged on vitamin D receptor genotype (JAMA Oncol. 2017;3:628-35). Among patients with prostate cancer, addition of vitamin D to chemotherapy was actually associated with poorer overall survival (J Clin Oncol. 2011;29:2191-8).

"SUNSHINE was a positive study. It was a very well carried out phase 2 trial with a significant progression-free survival benefit. Correlative analyses are ongoing, and these will be critical, looking at biomarkers, perhaps helping us identify those patients who will benefit," Dr. Cercek summarized. "I agree 100% with the investigators that a phase 3 study is warranted, and I look forward to it."

Study details

Patients in SUNSHINE were randomized to receive first-line modified FOLFOX chemotherapy and bevacizumab plus either high-dose vitamin D (oral vitamin D_3 8,000 IU/day for 2 weeks as a loading dose, followed by 4,000 IU/day) or low-dose vitamin D (oral vitamin D_3 400 IU/day) on a double-blind basis. The latter "is an amount you would find in a multivitamin and only increases plasma levels by about 3 ng/mL, thus serving as a useful active control" Dr. Ng noted.

Receipt of chemotherapy and bevacizumab was generally similar between groups. "It is interesting to note that more patients receiving high-dose vitamin D discontinued treatment to undergo potentially curative surgery compared to those in the control arm, though this was not statistically different," she noted.

In intent-to-treat analysis conducted at a median follow-up of 17-18 months, progression-free survival, the trial's primary endpoint, was a median of 13.1 months in the high-dose group and 11.2 months in the low-dose group (P = .04). The difference in favor of high-dose vitamin D remained significant in multivariate analysis (hazard ratio, 0.67; P = .02).

The groups were statistically indistinguishable with respect to overall response rate, but the disease control rate was marginally better with high-dose versus low-dose vitamin D (96% vs. 84%, P = .05).

Rates of most grade 3 or 4 adverse events did not differ significantly between groups. However, diarrhea of these grades was less common in the high-dose vitamin D group (1% vs. 12%; P = .02). With respect to grade 3 or 4 events possibly related to the vitamin therapy, there was one case of hyperphosphatemia in the high-dose group and one case of kidney stones in the low-dose group.

Dr. Ng disclosed that she receives honoraria from Prime Oncology and Sage Publications; has a consulting or advisory role with Defined Health and Genentech/Roche; and receives research funding from Celgene, Genentech/Roche (institutional), Gilead Sciences, Pharmavite (institutional), and Trovagene.

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FDA approves panel to identify patients for panitumumab tx

BY LUCAS FRANKI
Frontline Medical News

The Food and Drug Administration has approved the Praxis Extended RAS Panel for the identification of metastatic colorectal cancer patients who can be treated with panitumumab.

The Praxis Extended RAS Panel is able to detect 56 specific mutations in the RAS genes of mCRC patients, and is the first next-generation sequencing test approved by the FDA capable of testing more than one RAS gene mutation. If RAS mutations are not detected, then panitumumab is indicated, and if a mutation is detected, panitumumab is not indicated, according to the FDA statement.

Approval was based on a retrospective analysis of available samples from mCRC patients who were enrolled in a clinical trial evaluating panitumumab plus FOLFOX versus FOLFOX alone.

"Panitumumab's product labeling has been modified to align the indication for panitumumab and intended use for the Praxis Extended RAS Panel," the FDA noted.

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GI & HEPATOLOGY NEWS

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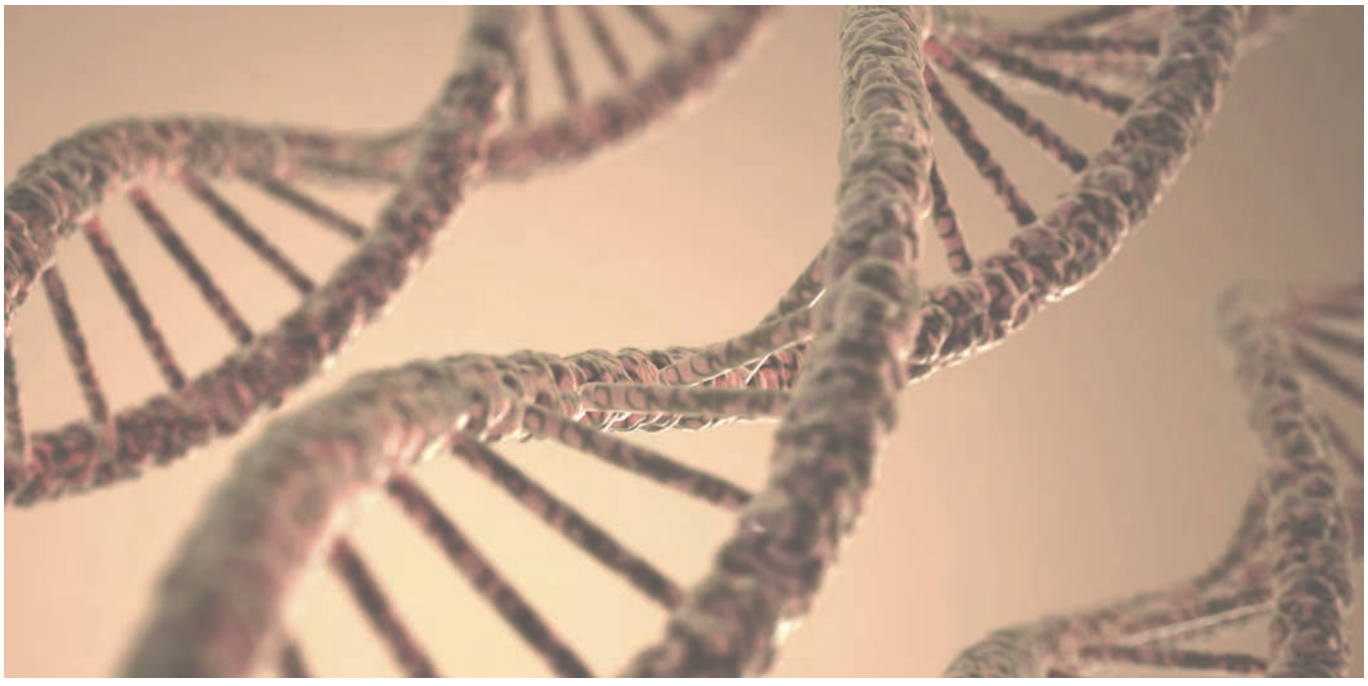
Relatives of NAFLD patients: 12-fold higher risk

BY MARY ANN MOON
Frontline Medical News



KTSIMAGE/THINKSTOCK

Asymptomatic first-degree relatives of patients who have nonalcoholic fatty liver disease (NAFLD) with cirrhosis are at a 12-fold higher risk for advanced liver fibrosis compared with the general population, according to a report published online June 19 in the Journal of Clinical Investigation.

If this preliminary but robust association is confirmed in further research, it may well change clinical practice. First-degree relatives would likely require screening for advanced fibrosis, and those found to have it would likely need continued surveillance for hepatocellular carcinoma.

Presumably, such screening and surveillance would allow more timely referral for liver transplantation, which would in turn improve patient survival, said Cyrielle Caussy, MD, PhD, of the NAFLD Research Center, University of California San Diego and the University of Lyon (France) and her associates.

They noted that previous studies have suggested a familial component to NAFLD, and decided to assess the risk of advanced fibrosis in first-degree relatives of patients who had NAFLD plus cirrhosis. The investigators used noninvasive imaging techniques – MRI-PDFF (MRI proton density fat fraction) and MRE (magnetic resonance elastography) – to quantify liver fat and liver fibrosis in 26 patients who had NAFLD plus cirrhosis, 39 of their first-degree relatives who were asymptomatic, 69 community-dwelling adults who did not have NAFLD or cirrhosis, and 69 of their first-degree relatives.

The primary outcome measure, the prevalence of advanced liver fibrosis, was 18% among first-degree relatives of patients who had NAFLD plus cirrhosis. This was markedly greater than the prevalence of advanced fibrosis among first-degree relatives of unaffected adults (1.4%).

The odds ratio of having advanced fibrosis among first-degree relatives of affected patients was 14.9, compared with the control population. When the data were adjusted to account for age, sex, body mass index, and diabetes status, the OR remained statistically and clinically significant at 12.5, Dr. Caussy and her associates said (doi.org/10.1172/JCI93465).

This study was limited in that it was a single-center investigation and used advanced MRI techniques that may not be routinely available at other centers. In addition, since it was cross-sectional in design, long-term outcomes, such as the development of hepatocellular carcinoma and survival rates, could not be assessed.

"Despite these limitations, we believe that this study provides important data that require validation in larger studies to then change clinical practice guidelines to screen first-degree relatives of patients with NAFLD with cirrhosis," the investigators added.

The National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Environmental Health Sciences supported the study. Dr. Caussy and her associates reported having no relevant financial disclosures.

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Liver disease doubles risk of colorectal cancer

BY MARY ANN MOON
Frontline Medical News

Chronic liver disease appears to double the risk of colorectal cancer (CRC), even after patients undergo liver transplantation, according to a report published in Gastrointestinal Endoscopy.

"Strict surveillance for colorectal cancer is warranted in this patient population," said Yuga Komaki, MD, of the section of gastroenterology, hepatology, and nutrition, University of Chicago, and associates.

One prominent chronic liver disease, primary sclerosing cholangitis, is known to raise the risk of CRC, which "is mainly attributed to the concurrence of inflammatory bowel disease." In addition, whether liver transplantation mitigates that risk remains "controversial," the investigators noted.

To assess whether chronic liver disease impacts CRC risk, they performed a systematic review and meta-analysis of the literature, examining data from 55 observational studies involving 55,991 participants. Case patients had a variety of chronic liver diseases, including primary sclerosing cholangitis, viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, and alcoholic liver damage.

Overall, the pooled standardized incidence ratio of CRC was 2.06 among patients with liver disease, compared with control subjects. It was highest in the subgroup of patients with primary sclerosing cholangitis at 6.70, the investigators said (Gastrointest Endosc. 2017;86:93-104).

CRC risk appeared to be slightly higher among patients who had cirrhosis than among those who had hepatitis, "suggesting that advanced liver damage may lead to higher risks of CRC. This is not surprising because advanced liver damage can cause systemic alterations in immunity," Dr. Komaki and associates noted.

The pooled standardized incidence ratio of CRC remained elevated at 2.16 among patients who underwent liver transplantation for a variety of causes. It is possible that their exposure to immunosuppressive therapy plays a role in elevating this risk, the researchers added.

"We propose that patients with chronic hepatitis and cirrhosis require a screening colonoscopy every 5 years, as opposed to the 10-year interval in the general population. Patients undergoing liver transplant should have a colonoscopy before the transplant and, subsequently, should undergo colonoscopy at 5-year intervals," Dr. Komaki and associates said.

They added that the sixfold increase in CRC risk among patients with primary sclerosing cholangitis "justifies the present recommendation of annual surveillance colonoscopy that should be continued after transplant."

No specific sponsor was identified for this study. Dr. Komaki reported receiving research support from the Children's Cancer Association of Japan. Dr. Komaki and associates reported having no other relevant financial disclosures.

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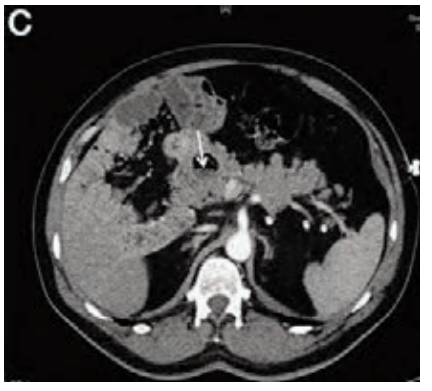
CLINICAL CHALLENGES AND IMAGES

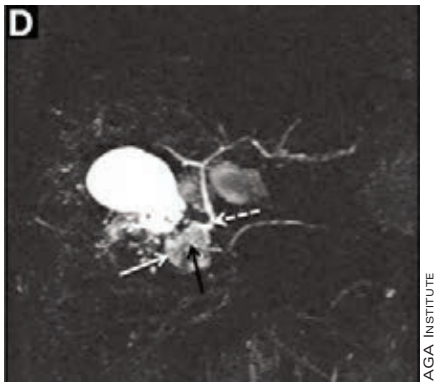
The diagnosis

Answer to "What's your diagnosis?" on page 2: Lemmel's syndrome

Figure C shows a 30 × 22–mm juxtapapillary diverticulum (JPD) containing air, fluid, and food debris (white arrow). Figure D shows the JPD (solid white arrow) causing distortion of a normal-caliber distal common bile duct (dashed white arrow) and pancreatic duct (PD; black arrow), with no gallbladder or ductal stones demonstrated. The final diagnosis was cholangitis and pancreatitis associated with a JPD without choledocholithiasis (Lemmel's syndrome). He remains well 2 months later on follow-up, with normal blood tests.

Duodenal diverticuli occur commonly (15%–20% of autopsies), especially in the elderly, are usually discovered incidentally, and mostly asymptomatic. The majority (75%) are periampullary; those located within 2–3 cm of the ampulla of Vater are called JPD. Patients may rarely present with symptoms including abdominal pain, steatorrhea, gastrointestinal bleeding, perforation, intestinal obstruction, diverticulitis, and cholangiopancreatic disease (obstructive jaundice, cholangitis, and pancreatitis).[1] Primary choledocholithiasis occurs commonly (incidence 20%–40%) in patients with periampullary duodenal diverticuli, owing to the production of beta-glucuronidase–producing microorganisms. However, many patients (up to 41%) with JPD and cholangiopancreatic symptoms have normal biliary and pancreatic ducts on cholangiography.[1,2] Lemmel's syndrome is the combination of JPD and cholangiopancreatic disease without choledocholithiasis.[3] It is postulated to arise from the reflux of duodenal contents with intestinal bacteria into the common bile duct and pancreatic duct, mechanical compression, or distortion of the distal common bile duct and pancreatic duct arising from an impacted enterolith or food debris in the diverticulum, or sphincter of Oddi dysfunction, with resultant bile stasis.[1] Patients characteristically describe postprandial epigastric pain or fullness. The mainstay of treatment in the majority of patients is conservative, although endoscopic removal of impacted food debris may occasionally be necessary. Operative intervention, preferably duodenojejunostomy, may be indicated for persistent/recurrent symptoms or severe complications (such as recurrent cholangitis/pancreatitis, bleeding, or perforation).





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EASL publishes new PBC guidelines

BY LUCAS FRANKI
Frontline Medical News

The European Association for the Study of the Liver has published a new guideline for the diagnosis, treatment, and management of primary biliary cholangitis.

PBC is likely in patients with persistent cholestatic symptoms or who have pruritus and fatigue. A diagnosis of PBC can be made if a patient has elevated alkaline phosphatase and antimitochondrial antibody, although elevated antimitochondrial antibody alone is not enough to diagnose PBC. Liver biopsy is not recommended, and liver imaging is not necessary to prove PBC but can eliminate extrahepatic causes of cholestasis.

Oral ursodeoxycholic acid (UDCA) is the most common and the recommended way to treat PBC, as it has been proven to be safe and effective for both pregnant women and nonpregnant individuals. A dosage of 13-15 mg/kg per day has been shown to be most effective for PBC treatment. An alternative licensed treatment is obeticholic acid, recommended in tandem with UDCA for patients with inadequate response to UDCA and as monotherapy for those intolerant to UDCA.

Pruritus, fatigue, and sicca complex are the most common symptoms of PBC and can significantly effect quality of life. Pruritus can be treated with cholestyramine or rifampicin. Caregivers should seek out and treat associated and alternative causes of fatigue and advise patients on strategies to avoid compounding fatigue problems. Sicca complex should be treated appropriately and, if patients develop refractory symptoms, referred to a specialist.

Complications of liver disease caused by PBC include osteoporosis, fat-soluble vitamin deficiency, hyperlipidemia, varices, hepatocellular carcinoma, and need for liver transplant, though the need for liver transplant in PBC patient has decreased over time.

Find the full clinical guideline in the Journal of Hepatology (2017. doi: 10.1016/j.jhep.2017.03.022).

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Multiply recurrent *C. difficile* infection is on the rise

BY DAN WATSON
Frontline Medical News

A retrospective cohort study of *Clostridium difficile* infection (CDI), the most common health care–associated infection, found that multiply recurrent CDI (mrCDI) is increasing in incidence, disproportionately to the overall increase in CDI.

Researchers from the University of Pennsylvania, Philadelphia, worked with a database of more than 38 million individuals with private health insurance between January 2001 and December 2012.

Cases of CDI and mrCDI in the study population were determined through ICD-9 diagnosis codes, and prescriptions for treatment. For the definition of mrCDI to be met, there had to be at least three courses of treatment lasting at least 14 days each.

In the study population, 45,341 persons developed CDI, of whom 1,669 had mrCDI. The median age was 46 years, and 58.9% were female.

Between 2001 and 2012, CDI incidence increased by 42.7% ($P = .004$), while mrCDI incidence increased by 188.8% (P less than .001).

With increases in CDI and mrCDI incidence, and with the effectiveness of standard antibiotic treatment decreasing with each

Continued on following page

PERSPECTIVE

This study's findings may be understated

The retrospective cohort study was based on administrative data rather than laboratory data, Sameer D. Saini, MD, MS, and Akbar K. Waljee, MD, noted in an editorial accompanying the study. Further, with Medicare patients excluded from the study (because Medicare data were not available for the full time period studied for private insurance data), the data may not be of relevance to patients older than age 65 years.

But the general conclusion that both CDI and mrCDI are on the rise is a crucial matter. "We must first have a better understanding of mrCDI, its scope and epidemiology, and its associated risk factors. The study by Ma and colleagues begins this important work. A better understanding of the epidemiology of mrCDI is a critical first step toward developing a sound strategy to address this growing public health challenge."

Dr. Saini and Dr. Waljee are with the VA Ann Arbor (Michigan) Center for Clinical Management. Their editorial accompanied the study in Annals of Internal Medicine (2017 Jul. doi: 10.7326/M17-1565).

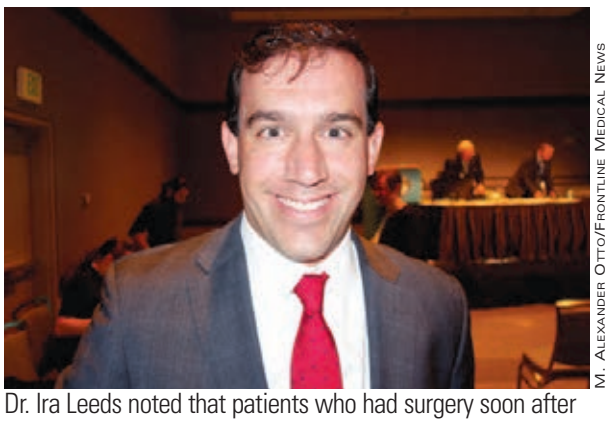
Sooner is better than later for acute UC surgery

BY M. ALEXANDER OTTO
Frontline Medical News

SEATTLE – Postponing surgery for acute ulcerative colitis more than a day increases postoperative complications, lengths of stay, and hospital costs, according to a review by Johns Hopkins University, Baltimore, of almost 2,000 patients.

It's not uncommon to wait 5 or even 10 days to give biologics a chance to work when patients are admitted for acute ulcerative colitis (UC). Based on the review, however, "we believe that the need for prolonged medical therapy and resuscitation in this patient population prior to colectomy may be overstated," and that "the lasting effects of persistent inflammation cascade are underestimated." There has to be "a conversation with the gastroenterologist to strike the right balance between medical and surgical therapy. Early surgical intervention" should be considered, lead author and general surgery resident Ira Leeds, MD, said at the American Society of Colon and Rectal Surgeons annual meeting.

AGA Resource
Visit www.gastro.org/ibd for patient education guides that you can share with your patients to help them understand and manage their ulcerative colitis and IBD.


M. Alexander Otto/Frontline Medical News

Dr. Ira Leeds noted that patients who had surgery soon after admission were probably sicker, but had fewer complications.

The team reviewed 1,953 index UC admissions with emergent nonelective abdominal surgery in the National Inpatient Sample (NIS) database from 2008 to 2013; 546 patients (28%) had early operations – within 24 hours of admission – and the other 1,407 had operations after that time.

Although it's impossible to say for sure given the limits of administrative data in the NIS, patients who had surgery soon after admission were probably sicker. Even so, they were less likely to have complications than patients in the delayed surgery group (55% versus 43%), and they had shorter hospital stays, with just 8% in the hospital past 21 days, versus 29% of patients who had delayed operations. The findings were similar for both overall length of stay and post-op length of stay.

Renal complications (8% versus 14%), pulmonary complications (20% versus 25%), and thromboembolic events (4% versus 6%) were also less common in the early surgery group. On multivariable analysis, delayed surgery increased the complication rate by 64%.

With fewer complications and shorter hospital stays, early operations were also less expensive, with a mean total hospitalization cost of $19,985 versus $34,258. The findings were all statistically significant.

Dr. Leeds noted the limits of the study; medical management regimes and the reasons for variations in surgical timing are unknown, among other things. "This is not the final answer on what to do with patients like this, but it opens the door to prospective studies that could control" for such variables, he said.

Early surgery patients were more likely to be male (57% versus 51%) and from households with incomes higher than the national median. There were no difference in age, race, comorbidities, region, or hospital type between the two groups.

Dr. Leeds said he had no disclosures.

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Loop ileostomy tops colectomy for IBD rescue

BY M. ALEXANDER OTTO
Frontline Medical News

SEATTLE – Diverting loop ileostomies save patients with inflammatory bowel disease (IBD) with severe colitis from rushed total abdominal colectomies, buying time for patient optimization before surgery, and perhaps even saving colons, according to a report from the University of California, Los Angeles.

Urgent colectomy is the standard of care, but it's a big operation when patients aren't doing well. Immunosuppression, malnutrition, and other problems lead to high rates of complications.

In 2013, UCLA physicians decided to try rescue diverting loop ileostomies (DLIs), a relatively quick, minimally invasive option to temporarily divert the fecal stream, instead. The idea is to give the colon a chance to heal and the patient another shot at medical management and recovery before definitive surgery. There's even a chance of colon salvage.

The approach has been working well at UCLA. Investigators previously reported good results for their first eight patients. They presented updated results for the series – now up to 34 patients – at the annual meeting of the American Society of Colon and Rectal Surgeons.

So far, DLI allowed 91% of patients (31/34) to avoid urgent total colectomies. It's "a safe alternative. Patients undergoing DLI have acceptably low complication rates and most are afforded time for medical and nutritional optimization prior to proceeding with their definitive surgical care," said presenter Tara Russell, MD, a UCLA surgery resident.

"Currently, [almost every] patient presenting with acute colitis who we aren't able to get to the point of discharge with medical optimization" is now offered rescue DLI at the university, and patients have been eager for a chance at avoiding total colectomy. The only patients who are not offered DLI are those with, for instance, fulminant toxic megacolon, Dr. Russell said.

The DLI approach failed in just 2 of the 18 ulcerative colitis patients and 1 of the 16 Crohn's patients in the series. All three went on to emergent total colectomies 11-53 days after the procedure.

The majority of DLI patients tolerated oral intake by postop day 1, and the median time to resuming a regular diet was 2 days. Most people were discharged within a day or 2 of diversion, and a few took longer to achieve medical rescue. Almost 90% had an improvement in nutritional status, and over 80% went on to elective laparoscopic definitive procedures or colon salvage.

Two patients had postop wound infections, "but there were no other complications" with DLI, Dr. Russell said.

All of the DLIs were performed with a single-incision laparoscopic approach and took an average of about a half hour. Most of the diversions were in the right lower abdominal quadrant.

The mean age of the patients was 36 years, with a range of 16-81 years. Just over half were men. Of 21 patients who met systemic inflammatory response syndrome criteria at the time of operation, 13 (62%) resolved within 24 hours of DLI.

The presenter had no relevant financial disclosures.

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Continued from previous page

recurrence, "demand for new antimicrobial therapies and FMT [fecal microbiota transplantation] can be expected to increase considerably in the coming years," wrote Gene K. Ma, MD, and his coauthors.

As for FMT, the researchers noted that its likely greater demand in the future (as suggested by their study results) highlights the importance of establishing the long-term safety of the procedure (Ann Intern Med. 2017 Jul. doi: 10.7326/M16-2733).

With increases in CDI and mrCDI incidence, and with the effectiveness of standard antibiotic treatment decreasing with each recurrence, "demand for new antimicrobial therapies and FMT can be expected to increase considerably in the coming years."

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Reference: 1. Clinical decision support tools. American Gastroenterological Association website. http://campaigns.gastro.org/algorithms/constipation/index.html. Accessed May 12, 2017.

Elderly black individuals at higher risk of CRC

BY MOLLIE KALAYCIO
Frontline Medical News

Elderly black patients on Medicare are at a 31% higher risk for colorectal cancer (CRC) than white patients, according to a study done by Stacey A. Fedewa, PhD, MPH, and her colleagues at the American Cancer Society.

There were 2,735 cases of interval CRC identified between 2002 and 2011 for this study. The patients studied were between 66 and 75 years of age and were all enrolled in Medicare. A higher proportion of black individuals, 52.8%, received a colonoscopy from physicians with a lower polyp detection rate (PDR, a proxy for adenoma detection rate), compared with whites at 46.2%. The PDR, the number of patients in whom a polypectomy is performed divided by the number of colonoscopies performed in a 5-year period, is significantly associated with interval CRC risk (Ann Intern Med. 2017. doi: 10.7326/M16-1154).

Interval CRC, defined as cancer that develops after a negative result on colonoscopy but before the next recommended test, accounts for 3%-8% of CRC cases in the United States. These cases of CRC develop in certain populations because they were missed at the time of screening or between recommended screenings or surveillance intervals.

Results showed that the probability of interval CRC by the end of follow-up was 7.1% in blacks, 5.8% in whites, 4.4% in Hispanics, and 3.8% in Asians. Of the 79,396 Medicare patients that met enrollment criteria, 61,433 were included in the study. The average age of index colonoscopy was 70 years, and 2,735 cases of interval CRC were identified.

"Future studies examining this issue are warranted, given the higher overall risk for interval CRC in black populations as well as the larger disease burden in this group," Dr. Fedewa said.

A higher proportion of black individuals, 52.8%, received a colonoscopy from physicians with a lower polyp detection rate (a proxy for adenoma detection rate), compared with whites at 46.2%. Results showed that the probability of interval CRC by the end of follow-up was 7.1% in blacks and 5.8% in whites.

Medicare patient data were gathered from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER), a data collection of 18 cancer registries across the United States. Claims data were used to identify receipt and dates of patient colonoscopies and polypectomies, as well as the PDR of administering physicians. Data from SEER were used to identify cases of interval CRC. Medicare Enrollment data were used to determine patients' ethnicities.

The primary exposures were ethnicity and physician PDR, a relative measure of colonoscopy quality. Ethnicities were categorized as non-Hispanic white, black, Hispanic, Asian, and other. Patients were followed until they died, were no longer enrolled in Medicare, or experienced interval CRC defined as a first case of primary invasive CRC diagnosed 6-59 months after the colonoscopy.

The study was funded by the American Cancer Society and approved by the Institutional review board at Emory University. Data analysis for this research was supported by the American Cancer Society. Dr. Doubeni's contribution was supported by an award from the United States National Cancer Institute of the National Institutes of Health. Authors have declared no conflicts of interest.

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DDSEP eight Digestive Diseases Self-Education Program

Quick Quiz answers

Q1: Answer B

This patient has chronic hepatitis E infection, as demonstrated by the positive hepatitis IgG antibody. It is recommended that HEV RNA be identified in serum or stool for diagnosis of hepatitis E. However, HEV RNA PCR is not readily available outside of research settings and therefore the Centers for Disease Control and Prevention states that the diagnosis can be confirmed only by testing for the presence of antibody against HEV or HEV RNA. Providers must be aware of the possibility of false positives and negatives for HEV serologies.

In immunocompetent individuals, hepatitis E is generally a self-limited condition, but in solid-organ transplant recipients, chronic infection can ensue. Hepatitis E infection in solid-organ transplant recipients has been linked to consumption of game meat, pork, and mussels. The infection is largely asymptomatic, but occasionally presents with jaundice. The liver test elevations are mild, with ALT levels up to 300 U/L. Approximately 60% of transplant recipients who are infected with hepatitis E develop chronic infections.

The best treatment for chronic hepatitis E in solid-organ transplant recipients is ribavirin. In one study, the sustained virologic response rate was 78% after a course of approximately 3 months of ribavirin. Pegylated interferon has been used for treatment of hepatitis E, but has less evidence to support its use and has a less favorable side effect profile. Sofosbuvir is a treatment for hepatitis C and therefore is not correct, though there are recent data suggesting that sofosbuvir inhibits hepatitis E virus replication in vitro and results in an additive effect when combined with ribavirin.

Observation is not a correct answer, as about 10% of patients with chronic hepatitis E may develop cirrhosis. Although not one of the provided answers, lowering the overall immunosuppression would be part of the treatment approach in a solid-organ transplant recipient with chronic hepatitis E.

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Q2: Answer D

The history of weight loss, intermittent diarrhea, and bloating are suspicious for celiac disease. While lactose intolerance can explain the pain, diarrhea, and bloating, there does not appear to be any correlation with the ingestion of particular foods, nor should there be any weight loss. While inflammatory bowel disease is certainly a possible explanation for his symptoms, it would be premature to jump to upper and lower endoscopy as initial evaluations.

Tissue transglutaminase antibodies are a sensitive and specific screening test for celiac disease, with published sensitivities and specificities greater than 95%. Obtaining a total serum IgA level at the time of screening is recommended to exclude IgA deficiency, which may result in a false-negative test.

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AGA Institute Presidential Plenary

THESE PRESENTATIONS WERE GIVEN AT DIGESTIVE DISEASE WEEK® 2017

Hepatitis B elimination: Is it possible?

BY ANNA S. LOK, MD, DSC, AGAF

Despite the availability of safe and effective vaccines for more than three decades, the 2017 World Health Organization (WHO) Global Hepatitis Report estimated that worldwide more than 250 million persons are chronically infected with hepatitis B virus (www.who.int/hepatitis/publications/global-hepatitis-report2017/). In the United States, as many as 2.2 million persons may be chronically infected but only one-third are aware of their infection. In 2015, the WHO declared that hepatitis B and C should be eliminated as public health problems by the year 2030. In March 2017, the National Academies of Science, Engineering and Medicine (NASEM) set targets for HBV elimination in the United States by 2030 as follows: 50% reduction in deaths, 45% reduction in cirrhosis, and 33% reduction in hepatocellular carcinoma (HCC) compared to 2015 (www.nationalacademies.org/hmd/Activities/PublicHealth/NationalStrategyfortheElimination-ofHepatitisBandC.aspx). For these targets, 90% of persons chronically infected need to be diagnosed, 90% of those diagnosed linked to care, and treatment initiated in 80% of those with treatment indications. In addition, new infections among children should be eliminated through complete prevention of mother-to-child transmission.

The HBV elimination goals set by WHO and NASEM are lofty but feasible if all stakeholders make elimination of HBV a priority.

DR. LOK

HBV vaccination, particularly when initiated in newborns, is the most effective method of preventing HBV infection and its sequelae because the risk of chronicity is around 90% when infection occurs in newborns. Countries in which universal vaccination of newborns was initiated in the 1980s have witnessed a marked decline in HBV infection as well as HBV-related HCC in children and young adults. However, while 96% of countries worldwide have initiated nationwide HBV vaccine programs for infants, global birth dose coverage is only 39%, leaving many infants susceptible to infection during the first few months of life. Recent studies showed that administration of hepatitis B immunoglobulin and HBV vaccine within 24 hours of birth is inadequate in preventing infection of infants born to carrier mothers with high viremia. Antiviral medicine administered to highly viremic mothers during the third trimester of pregnancy is necessary to completely prevent the risk of mother-to-child transmission (Hepatology. 2016;63:261-83).

For persons who are chronically infected, antiviral therapy can suppress HBV replication, reduce hepatic inflammation, reverse hepatic fibrosis, and prevent progression to cirrhosis, hepatic decompensation, and HCC. However, currently approved treatments are associated with low rates of hepatitis B surface antigen (HBsAg) clearance and decreased but continued risk of HCC. New treatments aimed at cure are desired but complete cure of HBV may not be feasible as HBV persists in the liver even in patients with serologic recovery after transient acute HBV infection.

Functional cure aimed at restoring chronic hepatitis B patients to a state akin to those with spontaneous HBsAg clearance might be a more realistic goal. With improved understanding of the biology of HBV, including recent identification of its entry receptor, better in vitro and animal models, and revival of interest in hepatitis B research, it is conceivable that combinations of antiviral targeting different steps in HBV life cyle and immunomodulatory therapies

Continued on following page

AGA Institute Presidential Plenary

THESE PRESENTATIONS WERE GIVEN AT DIGESTIVE DISEASE WEEK® 2017

Sulindac-erlotinib as chemoprevention for FAP

BY N. JEWEL SAMADDER, MD, MSC, FRCP

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disorder caused by germline mutations in the APC (adenomatous polyposis coli)

This study lays a foundation for effective chemoprevention of colorectal adenomas in patients with FAP.

DR. SAMADDER

gene. The disease is characterized by the formation of hundreds to thousands of adenomatous polyps in the colorectum and a nearly 100% lifetime risk of colorectal cancer, if left untreated. Prophylactic colectomy has become the standard of care, once the extent of colorectal polyposis is beyond endoscopic control and abrogates the risk of colorectal cancer.

Six randomized clinical trials explore chemoprevention in FAP, including the use of sulindac, celecoxib, low-dose aspirin, eicosapentaenoic acid, and one ongoing trial using sulindac and difluoromethylornithine. These trials have shown at most a 30% decrease in colorectal adenoma burden over short-term treatment, compared with placebo.

Preclinical studies have shown that inactivation of the APC gene and epidermal growth factor receptor (EGFR) signaling promotes cyclooxygenase (COX)-2 expression and subsequent development of intestinal neoplasia. Our group has previously shown that the combination of COX and EGFR inhibition with sulindac and erlotinib led to a 71% reduction in duodenal polyp burden in patients with FAP.

The hypothesis of this study was that a combination of COX and EGFR inhibition would inhibit colorectal adenoma formation in patient with FAP. We designed a phase 2 double-blind, placebo-controlled randomized trial in FAP patients who received combination therapy with 150 mg sulindac b.i.d. and 75 mg erlotinib daily, or placebo tablets for 6 months and assessed the number of polyps in the colorectum, rectum, or ileal pouch at baseline and at 6 months.

The total colorectal polyp count was significantly different between the placebo and sulindac-erlotinib groups at 6 months in FAP patients with an intact colon (*P* less than .0001), with a net percentage change of 89.3% between the two groups. Similar reductions were found in the ileal pouch anal anastomosis and ileorectal anastomosis groups.

The total colorectal polyp count was significantly different between the placebo and sulindac-erlotinib groups at 6 months in FAP patients with an intact colon (*P* less than .0001), with a net percentage change of 89.3% between the two groups. Similar reductions were found in the ileal pouch anal anastomosis and ileorectal anastomosis groups. Major side effects were rash and diarrhea, with none exceeding grade 2. This study lays an important foundation for effective and feasible chemoprevention of colorectal adenomas in patients with FAP, which has the potential to decrease the need for endoscopic treatment and surgical intervention.

Further research is necessary to evaluate these preliminary findings in a larger study population with longer follow-up to determine whether the observed effects will result in improved long-term clinical outcomes. A new phase 2 multicenter clinical trial (sponsored by the National Cancer Institute) of erlotinib therapy in patients with FAP will be activating this summer across seven U.S. cancer centers and will add further evidence for this chemoprevention strategy.

Dr. Samadder is in the division of gastroenterology and hepatology, Mayo Clinic, Scottsdale, Ariz.

Continued from previous page

aimed to boost T-cell response to HBV and/or remove inhibitory signals can result in functional cure (HBsAg clearance) in a high percentage of patients after a finite course of treatment (Hepatology 2017; in press).

The HBV elimination goals set by WHO and NASEM are lofty, but as both organizations stated, these goals are feasible if all stakeholders make elimination of HBV a priority and allocate resources to make it happen.

Dr. Lok is the Alice Lohrman Andrews Research Professor in Hepatology in the department of internal medicine, University of Michigan Health System in Ann Arbor.

AGA Institute Presidential Plenary

THESE PRESENTATIONS WERE GIVEN AT DIGESTIVE DISEASE WEEK® 2017

Relamorelin for diabetic gastroparesis: Trial results

BY MICHAEL CAMILLERI, MD, AGAF

Gastroparesis is defined as delayed gastric emptying with associated symptoms in the absence of mechanical obstruction. The cardinal symptoms are upper abdominal pain, postprandial fullness, bloating, early satiety, nausea, and, with more severe disease, vomiting. Weight loss, malnutrition, dehydration, electrolyte imbalance, bezoar formation, and aspiration pneumonia may occur in advanced cases. Unfortunately, there are few approved or efficacious treatment options for diabetic gastroparesis. The 5-HT_4 receptor agonist, cisapride, has been withdrawn from the prescription markets in most countries.

Relamorelin demonstrated substantially improved core symptoms of diabetic gastroparesis.

DR. CAMILLERI

Relamorelin (RM-131) is a selective pentapeptide ghrelin receptor agonist with potent prokinetic properties. A prior phase 2a study showed that 10 microg b.i.d. relamorelin subcutaneously for 4 weeks had prokinetic activity and relieved symptoms of diabetic gastroparesis, especially in patients with vomiting at baseline.

The study aim was to evaluate the efficacy of relamorelin on disease symptoms and gastric emptying in moderate to severe diabetic gastroparesis. In a 12-week, double-blind, placebo-controlled, parallel-group, randomized, controlled trial, with a 2-week, single-blind placebo run-in, patients were randomized to 10 microg b.i.d., 30 microg b.i.d., 100 microg b.i.d., or placebo b.i.d. Patients completed a daily e-diary of symptoms (Diabetic Gastroparesis Symptom Severity Diary [DGSSD]: nausea, abdominal pain, postprandial fullness, and bloating on a 0–10 scale) and vomiting episodes, which were summarized by treatment week. The primary endpoint was a change from baseline in vomiting frequency; a key secondary endpoint was change from baseline in a four-symptom composite of DGSSD symptoms.

A longitudinal analysis over the 12-week trial showed there were reductions in nausea, postprandial fullness, abdominal pain, and bloating individually and as a composite score. Relamorelin accelerated gastric emptying $T_{1/2}$ at all three doses

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THESE PRESENTATIONS WERE GIVEN AT DIGESTIVE DISEASE WEEK® 2017

Developments in celiac disease and wheat-sensitivity disorders

BY SHEILA CROWE, MD, AGAF, AGA PRESIDENT

Celiac disease remained a rare disease until this century. "When I went to medical school, people from Ireland, the Netherlands, and other Northern Europeans had celiac disease. The prevalence of celiac disease has increased in the United States and worldwide.

The clinical expression of celiac disease has also changed over time. "In the past century, celiac disease was an overt malabsorptive condition with diarrhea, a low body mass index, bone disease, malnutrition, infertility, and anemia but atypical celiac disease is now common, with non-GI presentations including neurological problems, depression, and migraines. Many patients also lack an overt clinical manifestation – the so-called "silent celiac disase," which is often detected during screening of first-degree relatives and other at-risk patients.

Advances have been made in the understanding of celiac disease pathogenesis over the past few decades regarding the host genotype, currently restricted to the HLA genes, the delivery mode of gluten, type of feeding, time of feeding, and possibly antibiotics modulating the microbiome. The DQ2 genes are necessary but are insufficient to explain the development of celiac disease. About 40% of the burden of celiac disease is related to the HLA-DQ2.2, 2.5, and 8 genes. In spite of many genomewide association studies, no key molecules have been identified that play a significant role in causing the disease to date.

The association of enteric infections and celiac disease may explain why genetically susceptible individuals that are exposed to gluten from childhood do not all develop the disease in early childhood. The average age of diagnosis of celiac

About 40% of the burden of celiac disease is related to the HLA-DQ2.2, 2.5, and 8 genes.

DR. CROWE

disease in modern times is the mid-40s, and the individuals have been eating gluten all their lives, so it's not clear why and when people develop celiac disease. It has been postulated that enteric infection could modulate the immune system, cause breaches in the mucosal barrier, and alters of the microbiome, thus triggering the disease. A study recently published in Science supports the role of reovirus as a trigger for celiac disease and results from the TEDDY study group published in Clinical Gastroenterology and Hepatology suggest that rotavirus vaccination could reduce celiac disease autoimmunity in susceptible children.

While the mechanisms underlying nonceliac gluten sensitivity or wheat sensitivity are still unclear, the terms "encompass individuals who report symptoms or alterations in health that are related to perceived gluten or wheat ingestion." These symptoms could stem from fructose or fructans in wheat starch (FODMAPs), which could lead to symptoms similar to irritable bowel syndrome or other functional GI disorders. North American data show that more and more people without a diagnosis of celiac disease are consuming gluten-free products. Researchers have postulated that the pathophysiology of these conditions could include activation of the innate immune system, increased permeability, mucosal inflammation, basophil and eosinophil activation, antigliadin antibody elevation, and wheat amyloid trypsin inhibitors, but data have been inconsistent. The recommendation for diagnosing nonceliac gluten or wheat sensitivity is a double-blind placebo-controlled gluten trial to assess gluten-induced symptoms after excluding celiac disease or wheat allergy, but this testing is rarely available in North America. A recent study published in Clinical Gastroenterology and Hepatology demonstrated the limitations of this testing.

The gluten-free diet is now very popular, but some drawbacks have emerged. These include an increased risk for cardiovascular disorders linked to the diet according to a recent study published in BMJ, and increased levels of heavy metals in urine and blood found in insecticide used on rice, according to a recent study published in Epidemiology. Further studies are needed to corroborate these recall diet studies.

Dr. Crowe is a clinical professor of medicine in the department of gastroenterology, University of California, San Diego. She reports financial relationships with UpToDate, Fering, and Otsuka.

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compared with placebo. However, there were no effects on vomiting frequency, which showed a high placebo response. More hyperglycemia events and diarrhea events were observed with relamorelin treatment compared with placebo. The diarrhea reflects the previously demonstrated stimulation of colonic transit and motility and reduction of symptoms of constipation in patients with chronic constipation. The hyperglycemia likely resulted from accelerated gastric emptying rather than potential inhibition of insulin production, which has been reported with high levels of ghrelin in animal studies or with high levels of ghrelin associated with starvation.

Thus, relamorelin demonstrated substantially improved core symptoms of diabetic gastroparesis, was generally safe and well tolerated, and should be further assessed in pivotal phase 3 trials. The results in this trial suggest that there is no dose-response relationship between the three doses of relamorelin tested and that future trials of relamorelin might not need to include the 100-microg b.i.d. dose. Importantly, this study also suggests the importance to prospectively manage the hyperglycemia in future trials.

Dr. Camilleri is a faculty member in the department of gastroenterology and hepatology at the Mayo Clinic in Rochester, Minn.

AGA Institute Presidential Plenary

THESE PRESENTATIONS WERE GIVEN AT DIGESTIVE DISEASE WEEK® 2017

POEM versus pneumatic dilatation in therapy-naive patients with achalasia: Results of a trial

BY ARJAN BREDENOORD, MD

Patients with achalasia suffer from dysphagia and regurgitation caused by stasis of food in the esophagus because the lower esophageal sphincter has lost the ability to relax completely. Treatment is targeted at destroying the lower esophageal sphincter in order to enable passage of food to the stomach. Traditionally, treatment choices are pneumatic dilatation or Heller's myotomy. While many achalasia patients are adequately treated with these modalities, there are disadvantages such as potential complications and symptom recurrence (Gut. 2016;65[5]:732-9).

In 2010, per-oral endoscopic myotomy (POEM) was introduced by Haru Inoue, MD, as an alternative endoscopic treatment for achalasia patients (Endoscopy. 2010;42[4]:265-71). After the publication of his initial report describing 17 cases with good outcomes after POEM, there was a rapid uptake of the technique and since then many case series have been published describing excellent results in over 2,000 cases. However, all of these reports are case series without comparative treatment and most with a short follow-up (Neurogastroenterol Motil. 2014;26[1]:3-12). Data comparing POEM with the standard initial treatment, pneumatic dilatation, were lacking. We therefore developed a trial that allowed us to compare the efficacy of POEM with pneumatic dilatation as the initial treatment of therapy-naive patients with idiopathic achalasia.

Patients with achalasia newly diagnosed by high-resolution manometry (HRM) were randomized to POEM or pneumatic dilatations. Symptoms, including weight loss, dysphagia, retrosternal pain, and regurgitation, were assessed with the Eckardt score. Follow-up was planned at 3 months and 1 year after treatment. The primary outcome was therapeutic success (a drop in the Eckardt score to less than or equal to 3 in the absence of severe complications and need of retreatment). Secondary outcomes included integrated relaxation pressure (IRP) on HRM, barium column height on a timed barium esophagram, occurrence of complications, and the presence of reflux esophagitis on endoscopy.

These data show that, in therapy-naive idiopathic achalasia patients, POEM results in a significantly higher 1-year therapeutic success rate compared with pneumatic dilatations.

DR. BREDENOORD

One hundred thirty-three patients were randomly assigned to POEM (67) or pneumatic dilatations (66). Baseline characteristics were similar between groups regarding symptoms, age, sex, IRP, barium column height, and achalasia subtype. Three months after treatment, the success rate was 63/64 (98.4%) patients in the POEM group and significantly higher than the success rate of 52/66 (78.8%) patients in the group of patients treated with pneumatic dilatation. After 1 year, 59/64 (92.2%) patients were still in clinical remission after POEM, which is significantly higher than the 46/66 (70%) seen in patients after pneumatic dilatation. One perforation occurred after pneumatic dilatation with a 30-mm balloon, requiring endoscopic overstitching, antibiotics, and 13 days of hospitalization. Another patient was admitted for 1 night after pneumatic dilatation because of severe chest pain, a perforation was excluded. No severe adverse events occurred related to POEM treatment.

The patients who underwent POEM and pneumatic dilatation and were still in clinical remission at 1 year did not differ in IRP, barium column height, or symptoms as measured with the Eckardt score. Endoscopy at 1-year follow-up after patients stopped their proton pump inhibitors for at least 1 week showed that reflux esophagitis was significantly more evident in the patients treated with POEM (40.0% grade A/B, 8.3% grade C/D) than in those treated with pneumatic dilatations (13.1% grade A/B, 0% grade C/D).

These data show that, in therapy-naive idiopathic achalasia patients, POEM results in a significantly higher 1-year therapeutic success rate compared with pneumatic dilatations. However, development of reflux esophagitis is much more frequently seen after POEM. Our study shows that POEM should be added to the standard care of achalasia patients, but also underlines that patients should undergo an endoscopy at follow-up in order to screen for the presence of reflux esophagitis.

Dr. Bredenoord is a consultant gastroenterologist at the department of gastroenterology and hepatology, Academic Medical Center, Amsterdam.

Stress is just part of the picture

Burnout *from page 1*

symptoms in themselves. At the meeting, Laurie A. Keefer Levine, PhD, a GI health psychologist and the director of psychobehavioral research at the Icahn School of Medicine at Mount Sinai, New York, recounted the story of a medical student who jumped from her apartment building and killed herself.

"While she is not the first medical student to kill herself, this was an opportunity for the medical students to sit down and talk with the faculty," said Dr. Keefer Levine, noting that specifically it focused on how this young woman's distress had been missed, what was going on with students, and what is missing in medical education.

One of the main questions that came out of this discussion was why burnout isn't more readily recognized. "It had to do with our strength as medical professionals," she explained. "One common strength is that the pressure is self-generated, and we put a lot of pressure on ourselves to excel."

Health care providers are passionate about their work, and it is difficult to give up opportunities that are important to them. "We can delay gratification a really long time until research results come out, or wait a long time for that promotion," Dr. Keefer said, "But burnout is a very slow and insidious process. A lot of the time we don't recognize it, and we think 'just as long as we publish that paper,' everything will get better."

'Burnout is a very slow and insidious process. A lot of the time we don't recognize it.'

DR. KEEFER LEVINE

Also as time goes on, and physicians become more secure in their work and take on more responsibility, that becomes another avenue for burnout. But importantly, she emphasized, burnout can be confused with stress, and many people mistake encroaching burnout for stress.

There are pronounced differences between stress and burnout even though they can be co-occurring. The difference, Dr. Keefer explained, is that stress is a problem of too much – work, pressure, and so on, and it is an "overreaction" of the nervous system in that "we've got to get it done."

There is damage associated with chronic stress, but burnout is very different. Instead, burnout is a problem of "not enough."

"We do not have enough to mount necessary responses to deal with the stressors that we have," she said. "We are disengaged, our emotions are blunted. We feel helpless or hopeless and lose our motivation. And don't care about the things we were once passionate about. We don't have it in us any longer to contribute."

Physicians use any number of coping strategies, rather than recog-

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Persistent diarrhea:
are there faster diagnostic pathways?*

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

Current challenges

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

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

Convenient all-in-one testing is now available

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

Combines multiple stool and serum assays***

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

Addition of BAM assay provides a more complete view*

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

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

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

Tests for 14 types of pathogens

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

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

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

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

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

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

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nizing the problem. The unhealthiest coping strategy is venting. "We all do it, and it feels great, and it is meant to make us feel better," said Dr. Keefer Levine. "But if continues to happen over and over again, I would encourage you to think it through – that you are engaging in a coping strategy and may be missing burnout."

It is imperative that medical providers recognize burnout early on, and not wait until it is too late, when there may be major consequences, she said.

Arthur DeCross, MD, professor of medicine at the University of Rochester (N.Y.), discussed some of the subgroups of gastroenterologists who may be at the highest risk of burnout.

Gender plays a strong role, and female gastroenterologists were more likely to identify themselves as being burned out, compared to their male peers. "They may be at risk in the lower domain for a sense of personal accomplishment," said Dr. DeCross.

"There are respect issues that may come into play, as the literature shows," he said. "For example, women are more likely to be addressed by their first name by patients and their peers. Also, even at meetings such as this one, how many times is a female presenter simply introduced by her first name?"

There are implicit respect issues here, said Dr. DeCross. "How many times do we hear something like, 'and now the lovely Millie will present her findings on ...?' "

He noted that he didn't think that this lack of respect is intentional, but that it is happening. In addition, there is an issue of wages, and reported data show that women gastroenterologists earn 15% less than their male peers, he noted.

Women are more likely to have competing elements of family and career that put them on the slower track to promotion, he added.

The duration of one's career also figured into the equation. Burnout was more noticeable early in the career process, suggesting that physicians with young families may be facing more conflicts and stress, and this is an issue that needs to be further explored, he noted.

"Early in the career, there is also the stress of proving oneself," said Dr. DeCross.

Another contributor to burnout is when physicians spend an increasing amount of time on weekends and holidays doing work-related activities, along with an increase in internal regulatory burdens in the workplace.

Dr. DeCross sat down with DDW TV to talk about the results of the survey, which you can watch at http://www.gastro.org/news_items/physician-burnout-amongst-gastroenterologists. Join your colleagues to discuss this important topic in the AGA Community at http://ow.Ly/aYyh30diuq3.

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More than data are at risk

Health IT *from page 1*

look at the state of the health care IT in this country. The task force was mandated by the Cybersecurity Act of 2015 and formed in March 2016.

"The health care system cannot deliver effective and safe care without deeper digital connectivity. If the health care system is connected, but insecure, this connectivity could betray patient safety, subjecting them to unnecessary risk," according to the task force report. "Data collected for the good of patients and used to develop new treatments can be used for nefarious purposes such as fraud, identity theft, supply chain disruptions, the theft of research and development, and stock manipulation. Most importantly, cybersecurity attacks disrupt patient care."

Specifically, the task force recommended:

- Defining and streamlining leadership, governance, and expectations for health care industry cybersecurity.
- Increasing the security and resilience of medical devices and health IT.
- Developing the health care workforce capacity necessary to prioritize and ensure cybersecurity awareness and technical capabilities.
- Increasing health care industry readiness through improved cybersecurity awareness and education.
- Identifying mechanisms to protect research and development efforts and intellectual property from attacks or exposure.
- Improving information sharing of industry threats, weaknesses, and mitigations.

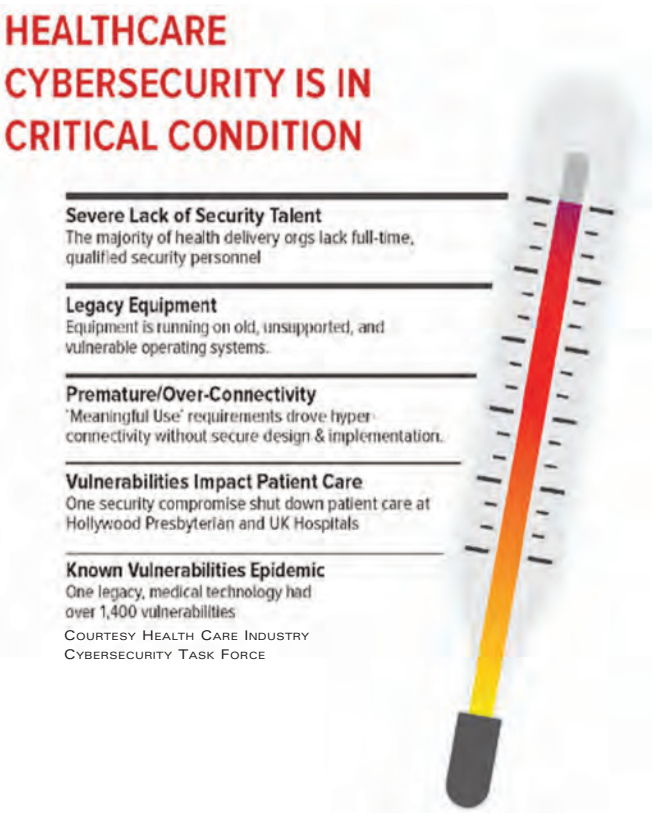
Health care cybercrime is a significant problem in the United States. In 2016, 328 U.S. health care firms reported data breaches, up from 268 in 2015, with a total of 16.6 million Americans affected, according to a report conducted by Bitglass (registration required), a security software company. In February 2016, a hospital in California was forced to pay about $17,000 in Bitcoin, an electronic currency that is known to be favored by cybercriminals, to access electronic health records that were held in a similar manner to last month's attack on the NHS.

For physicians, this may seem like someone else's problem; however, unsafe day-to-day interactions with connected devices and patient EHRs were among the task force's primary concerns.

Creating a safe password or not giving out critical information may seem like common sense, but many physicians are not able or willing to take the time to make sure they are interacting with systems safely, or they are overconfident in their security system, according to task force member Mark Jarrett, MD, senior vice president and chief quality officer at Northwell Health in New York.

"Phishing" is another concern. In a phishing scam, cybercriminals will pose as a fraudulent institution or individual in order to trick a target into downloading a virus, sending additional valuable information, or even paying money directly to the criminals.

"Physicians checking their emails need to be aware of possible phishing episodes, because they could be infected, and then there is the possibility that infection could be introduced into the system, Dr. Jarrett said. "I think the disconnect is [that physicians] are not used to [cybersecurity]. It's not part of their daily life and they also, up until recently, thought 'it's never going to happen to me.' "



"Health care workers often assume that the IT network and the devices they support function efficiently and that their level of cybersecurity vulnerability is low," according to the task force report.

This can be a costly assumption, financially, as well for safety; the price per stolen EHR averaged at $380 in 2016-2017, according to the Ponemon Institute's 2017 Cost of Data Breach Study, released in June. That is nearly triple the average cost of all breaches – $141– and higher than the price of $241 for information stolen from financial industries because, unlike a credit card number, patients' data are unique and cannot be replaced.

Aging equipment is another concern. Legacy software and machine systems used in medical practices and hospitals are not equipped with the necessary security services needed to handle the growing risks of connectivity, despite being included in the network.

"Every CT machine, every x-ray machine today is connected online, on one consolidated Internet" cybersecurity expert Idan Udi Edry of Trustifi said in an interview.

The cybersecurity task force report recommended creating health IT version of Cash for Clunkers, an Obama administration program that offered rebates to consumers who traded in older, less fuel efficient cars when purchasing a new car.

While experts agree that the growing focus on connected health care will continue to create cybersecurity risks, with all members of the health care industry working together, it is possible to keep hospitals and patients safe from would-be criminals.

The next key step is creating regulations that would encourage a cohesive structure of cybersecurity guidelines. According to the task force report, "a priority for regulatory agencies should be to ensure consistency among various federal and state cybersecurity regulations so that health care providers can focus on deploying their resources appropriately between securing patient information and the quality, safety, and accessibility of patient care" rather than having to focus on statutory and regulatory inconsistencies.

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PERSPECTIVE

WannaCry provides wake-up call

When computer hackers took control of the United Kingdom's National Health Service using a virus known as "WannaCry," doctors and nurses were left helpless, blocked from the files they would need to treat their patients until they paid to get them those files back.

Doctors were forced to revert to older methods, slowing everything to a snail's pace.

The media coverage of the event was dramatic, but there is no doubt the effects made it justifiably so.

NHS hospitals had not achieved their goal of being paperless; had they been, the service would have been completely unable to stop the attack.

It was not just software that was affected but medical devices as well. Physicians were unable to perform x-rays, and some hospitals found that the refrigerators used to store blood products were shut down.

While the NHS was particularly vulnerable to the WannaCry because of budget cuts, this cybercrime could have happened to any hospital, and its lessons are applicable for all.

Doctors do understand the value of patients' records, but they seem to be unaware of the physical harm that could befall patients from a cyberattack.

This attack needs to serve as a wake-up call for health care professionals who are not invested in their facilities' cybersecurity practices.

Underfunding left NHS hospitals terribly exposed, and if physicians continue to be complacent with how to handle this issue, the results are sure to be more severe.

Rachel Clarke, MD, is at Oxford (England) University Hospitals NHS Foundation Trust, and Taryn Youngstein, MD, is at Imperial College Healthcare NHS Trust, London. They reported having no relevant financial conflicts of interest. Their remarks were made in a perspective published in the New England Journal of Medicine (doi: 10.1056/NEJMp1706754).

PRACTICE MANAGEMENT TOOLBOX: From Obamacare to Trumpcare – implications for gastroenterologists

BY JOHN I. ALLEN, MD, MBA, AGAF

The June issue of CGH was the final column under my management. I have enjoyed the opportunity to provide you with information about practice management and health care reform. I also have enjoyed working with the Clinical Gastroenterology and Hepatology board of editors, and Erin Landis and Brook Simpson from AGA headquarters. Beginning in July 2017, this section will become the responsibility of Ziad Gellad, MD, MPH, AGAF, from Duke University. I have worked with Ziad for many years, and he serves on my board of editors for GI & Hepatology News. I have great confidence in his knowledge and ability.

DR. ALLEN

During the last 5 years, we have published 58 columns beginning with an article where I made several broad predictions. I have tried to present important concepts and management tools related to private and academic clinical practice, health care reform, and health economics. This article was written in early January 2017 just before the inauguration of Donald Trump. As I wrote, we did not know the full extent or the pace of "Repeal and Replace," as Obamacare becomes Trumpcare (www.healthaffairs.org/obamacare-to-trumpcare).

The extent of current Republican control of federal and state governments is unprecedented in modern political history. Per Newt Gingrich (The Economist, Jan. 7, 2017, p. 25), this will be the third attempt, after Ronald Reagan's election in 1980 and Gingrich's "Contract with America" in 1994, to break free from a "Big Government" mindset initiated by Franklin Roosevelt's New Deal. In this article, I will speculate how a right-leaning shift in American health care policy might impact the business model of gastroenterology. No matter how government regulations or funds flow change, we (physicians) will ultimately be responsible for digestive care provided to our patients. In the words of Martin Luther King Jr. (as he paraphrased Theodore Parker), "The arc of the moral universe is long, but it bends toward justice." What is remembered by fewer people, however, are words he then added during his speeches: "but only if we march."

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

The first column was published in July 2012.[1] I wrote about five dominant themes that would alter our gastroenterology practices in the ensuing years. They were 1) an increasing requirement for us to demonstrate value, 2) the need to think about population management in addition to individual patient care, 3) consolidation that would occur at all levels of health care delivery, 4) increasing cost pressure, and 5) how medical decisions would be linked to reimbursement (now called value-based payment). I fully expected the Patient Protection and Affordable Care Act (ACA) would shape the health care landscape for the rest of our careers. After the article's publication, I was invited to speak about health care reform at many academic centers and private practices. My last talk before the election was in Pasadena, Calif. (Oct. 28, 2016) where I confidently spoke about the

implications of President Clinton's cementing ACA into the fabric of U.S. medicine.

On Nov. 8, 2016, 136 million Americans (58% of eligible voters) handed an electoral college victory to the Republican presidential candidate and swept the Democratic Party out of power at almost all levels of government. We handed near complete governmental control to a conservative party whose stated goal is to devolve federal regulatory power to states, local governments, and individuals. Because most health care leaders have spent a generation building practice and advocacy efforts with a focus on Washington (mostly controlled by a progressive, Democratic agenda), we must now understand what impact this election will have on our patients, our health systems, our academic institutions, and our practices.

Donald Trump is now the 45th President of the United States. Republicans hold a 52-48 majority in the Senate and a 241-194 majority in the House. As of January 2017, one Supreme Court seat was available, and three more may open because of retirements (Justice Ginsburg is 83 years old, Justice Kennedy is 80, and Justice Breyer is 78). Republicans control all three branches of government in 25 states and dominate in 8 others. Conservative politicians control a large majority of county and city boards.

Until this year, Republicans have controlled all three branches of government only twice since 1945 (modern political history), and only once (George Bush in 2005) did the president have a Senate majority.[2] With his win, Mr. Trump can lead a conservative revolution to reverse key initiatives begun when the Democratic Party held majority power. Repeal of the ACA, signed into legislation on March 23, 2010, is the Republican Party's top priority.

Equally important, Congress can alter previously implemented federal regulations. Each year about 3,000 regulations are written by federal agencies that act with authority delegated by Congress (albeit Congress retains power to overturn them). Regulations are published in the Federal Register as preliminary rules during each year, and Final Rules are published after a public comment period and implemented shortly thereafter. Regulations carry the force of law and are codified in the Code of Federal Regulations. The Code of Federal Regulations is divided into 50 sections (Titles), with Title 42 (Public Health) and Title 45 (Public Welfare) most pertinent to us.

Other policies are created through executive orders, issued by the president (federal) or governors (states), without involvement of legislative or judicial branches (they were not mentioned in the Constitution, by the way). Executive orders issued by President Obama acould, theoretically, be overturned by new executive orders.

Repeal and replace

Destruction of the ACA is a top priority of President Trump and Republican leaders of both houses of Congress. The ACA was a Democratic bill (passed with no Republican support), although it had many similarities to previous Republican legislative ideas dating from 1993.[3]

Although outright repeal could be blocked by a Democratic filibuster, the law could be drastically modified through budget reconciliation whose passage takes only a simple Senate majority. Thus, a simple budget-related bill could serve as a vehicle to defund many parts of ACA, including money for Medicaid expansion, insurance risk corridors, money to offset out-of-pocket expenses and individual premium subsidies, for example.[4,5]

There would be substantial problems if ACA were repealed even with a 2- or 3-year delay, a scenario proposed to provide time for a replacement bill. On Jan. 4, 2017, the House Republican Study Committee introduced the American Health Care Reform Act (AHCRA) as a replacement proposal, with the stipulation that ACA would be repealed as of Jan. 1, 2018. This initial bill hinted at Republican intent and was detailed in a Health Affairs blog.[6] Importantly, there were distinct similarities between this and prior Republican proposals put forward by Representative Tom Price (nominated to head the Department of Health & Human Services under President Trump) and Speaker of the House Paul Ryan.[7,8]

Consistently, Republicans have advocated for expansion of health savings accounts, altering the tax code to allow individuals to deduct health insurance premiums, establishment of association risk pools, imposition of malpractice limits, protections for people with preexisting conditions, and further restrictions on abortion coverage. The AHCRA changes financial subsidies for purchasing insurance from a tax credit (which can be paid to people even if they do not pay taxes) to a tax deduction (only applicable to people who pay taxes). Analysis of a similar proposal made by President Trump during the campaign found that this plan would increase the number of uninsured people by more than 15 million.

If ACA is repealed, effects would be broader than just factors related to insurance coverage.[9] ACA provides for preventive care (including colonoscopy) without copays, education of additional medical personnel, closing the donut hole for Medicare Part D (medications), approval of generic biologics, and Medicaid expansions, among other initiatives. If ACA were defunded without restoring pre-ACA support for Disproportion Share Hospital charity care, research, and graduate medical education, then safety-net hospitals and many academic medical centers (AMCs) could face enormous funding cuts.[10] Defunding Medicaid expansion would adversely affect states in many ways, as pointed out by Ayanian et al.[11] Medicaid expansion had broad economic impact in states that accepted federal money to expand. In Michigan for example, 30,900 jobs were added to the state in 2016 because of Medicaid expansion, with two-thirds outside of the health care industry. President Obama defined his view about the effects of ACA repeal in the New England Journal of Medicine.[12]

Lessons learned

Economic principles and unique characteristics of United States health care help explain why solutions to its high cost and uneven coverage are so difficult to achieve. These include higher prices for goods in the United States compared with other countries, variation in price (unrelated to quality), restraints on government price negotiations, inefficiencies due to variation in size of delivery systems, and "moral hazard" related to rich insurance coverage, which are some of the factors that doom any simple solutions. These are reviewed by Victor Fuchs[13] in an excellent article in Annals of Internal Medicine. Payment methods for health care services also distort resource use and efficiencies. Understanding the eight basic payment methodologies in health care and current predictions about future health care spending will be important in shaping reimbursement policies.[14,15]

Disruptions in health care are unpopular and, as Uve Reinardt stated: "Our health care financing system will always remain a horrendous mess and a fountain for such dismay among the providers of health care as well as among patients."[4] Lessons to inform the next iteration of health care policy, learned from the 2009-2010 experience, might be as follows:

1. If a bill is to be passed, the president must personally lead in explaining the bill to the public in simple terms.
2. Even the threat of repeal may disrupt the current market and force insurance companies to exit quickly.
3. Coverage must be affordable to individuals, state budgets, and health care providers. Because expansion states saw positive impacts to state budgets[8] and mental health and substance abuse services became part of Medicaid benefits, how will a replacement bill maintain coverage and compensate for new state moneys used now for other imperatives such as education and infrastructure?
4. Health care is like a massive cargo ship, not a sports car, so a bill to replace the ACA may take a long time (and might never be passed).
5. Health care is intensely personal, so it will always be politically charged.

Ultimately, physicians will need to make strategic guesses and rapid adjustments to sustain financial viability and provide high-value care. Strategies differ depending on your practice situation. Keep in mind the five principles listed in the opening paragraph of this article. It is likely that the most important principle to factor into your practice strategy is continuing reduction in reimbursements. No matter what model is adopted to reform the ACA, the financial pot (Medicare, Medicaid, commercial insurance, bundled payments, fee-for-service payments) will be reduced, and the number of uninsured patients will increase. How would you change your practice if Medicare was your best payer ("manage to Medicare")?

Take-away points:

1. There are five dominant themes in medicine that will affect practices as outlined in the first paragraph. They remain pertinent no matter what happens politically.
2. The Republican Party continues to work toward repeal and replacement of the Affordable Care Act.
3. Should the ACA be repealed, many low-income Americans will lose coverage.
4. Alternatives to Medicaid and marketplace coverage are being considered, especially high-risk pools.

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Independent practices

Physicians in small- to medium-size independent practices continue to struggle with reducing reimbursements, reporting burdens, increasing overhead expenses, crushing regulatory requirements, and provider burnout. Trumpcare will favor small practices more than Obamacare from a policy (not necessarily a financial) perspective. Regulations on small business and reporting burdens may ease, but the move toward value-based reimbursement as outlined in the MACRA (passed with overwhelming bipartisan support) will not end.[16] Practices in small communities continue to thrive because they give excellent care with limited competition and low overhead. Some practices in suburban and urban centers struggle because payers tend to favor (with enhanced managed care rates) larger practices and health systems. Large, horizontally integrated, efficient gastroenterology practices will continue to thrive because they can develop a "must-have" position with payers. Building remote patient monitoring, teleconsulting, and capabilities around value demonstration will be strategically advantageous.

Options for independent physicians include 1) maintaining status quo, 2) retiring, or 3) exiting the independent business model through a practice sale. Traditionally, physicians who wanted to sell their practices turned to hospitals or health systems. Recently, a physician-run model funded by venture capital has emerged where reduced overhead (through centralization of services) is combined with enhanced power during payer negotiations (because of scale). This model has allowed practices to merge into a physician organization and remain free from health system employment.[17]

Large health systems

Physicians employed by large health systems, whether they are nonprofit, for-profit, or AMCs, will see their future tied directly to health system success. If bundled payment, alternative payment, and capitation models of health care financing continue to grow in popularity, then success will be determined by a health system's market share and its ability to form true clinical integration. In a capitated environment, expansion of market share (especially of relatively healthy patients) will help support margins. However, financial success will come from a system's ability to manage high-cost patients, those 5% of patients who consume 50% of health care resources.[18]

Hospitals with a financially challenged patient base (safety-net hospitals) will have enormous financial pressures going forward. Repeal of ACA without restoration of pre-ACA funding will affect directly the financial health of systems including AMCs. AMCs and other health systems will be forced to reduce fixed overhead, enhance productivity of faculty, and restrict nonfunded activities (teaching for example). Although most AMCs are now in an active acquisition mode, this strategy is naturally limited by the number of remaining acquisition targets. Traditional high managed care rates enjoyed by AMCs will shrink, as will federal research funding (which typically comes with high indirect financial support). Health systems and GI societies will need to dedicate much more attention to state policy makers as Trumpcare progresses.

Finally, all providers will need to manage the business implications of retail health. As people assume higher deductibles and copays and health savings accounts grow, patients will change their patterns of purchasing services. Reputation counts for less when people are facing large price differences, so attention to patient-centric amenities, price, patient engagement, and patient satisfaction will become even more important.

Conclusion

The United States has undergone a massive and rapid political trans-

formation. The mandate felt by conservative politicians, perhaps not supported by numbers, will carry a conservative platform forward. In areas where progressive Democrats emphasized federal power and socialized regulation (religion, education, civil rights, income security, and health policy), conservatives will transfer decision power as much as possible to states, local communities, and individuals. Maintaining the concept of "health as a right" will test the conscience of all of us.

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