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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

DOUG BRUNK/FRONTLINE MEDICAL NEWS

Dr. Kenneth Cusi said, "Patients with diabetes [type 2] face the greatest risk of fatty liver and of fibrosis."

Three in 10 diabetic patients may have liver fibrosis

BY DOUG BRUNK
Frontline Medical News

LOS ANGELES – For every 10 adult patients with type 2 diabetes, three are likely to have moderate to severe liver fibrosis, according to Kenneth Cusi, MD, FACP, FACE.

"The question is, How are we going to tackle this problem? My academic goal is that we incorporate screening for NASH [nonalcoholic steatohepatitis], or for fibrosis more specifically, in the same way we do for retinopathy or nephropathy [in diabetes], because we do have a way to treat it," he said at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease.

Dr. Cusi, chief of the division of endocrinology, diabetes, and metabolism at the University of Florida, Gainesville, predicted that obesity will become the No. 1 cause of liver transplantation. "It's a real epidemic; you're not seeing it because the inflexion of obesity happened just 2 decades ago," he said. "Patients with diabetes face the greatest risk of fatty liver and of fibrosis. Untreated, it's the equivalent of having macroalbu-

See **Fibrosis** · *page 25*

Many drugs in the pipeline for IBD treatment

BY DOUG BRUNK
Frontline Medical News

LAS VEGAS – A wide variety of drugs are in the pipeline for both ulcerative colitis (UC) and Crohn's disease patients who are failing currently available therapies.

"The challenge for all of us is to integrate the right drugs for the right patients," William J. Sandborn, MD, AGAF, said at the annual congress of the Crohn's & Colitis Foundation, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association.

Dr. Sandborn, professor and chief of the division of gastroenterology at the University of California, San Diego, began his presentation by highlighting anti-integrin therapies for inflammatory bowel disease (IBD) treatment. These leukocyte membrane glycoproteins target beta1 and beta7 subunits. They interact with endothelial ligands VCAM-1, fibronectin, and MadCAM-1, and mediate leukocyte adhesion and trafficking. Approved anti-integrin therapies to date include natalizumab and vedolizumab, while investigational therapies include etrolizumab, PF-00547659, abrilumab, and AJM 300.

In a phase 2 study of etrolizumab as induction therapy for moderate to severe UC, Séverine Vermeire, MD, AGAF, Dr. Sandborn, and associates randomized 124 patients to one of two dose levels of subcutane-

See **Pipeline** · *page 22*

INSIDE

New multi-analyte blood test shows promise screening for several cancers

BY SHANNON AYMES
Frontline Medical News

Imagine a single blood test that would cost less than $500 and could screen for at least eight cancer types.

It's early days for the technology, called CancerSEEK, but the test had a sensitivity of 69%-98%, depending on the cancer type, and a specificity of 99% in a cohort of 1,005 patients with stage I-III cancers and 850 healthy controls, wrote Joshua D. Cohen of the Ludwig Center for Cancer Genetics and

See **Blood test** · *page 34*

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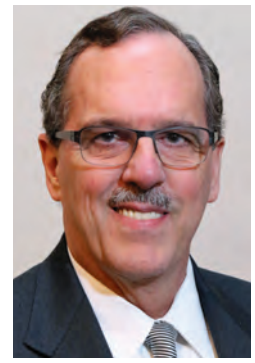
LETTER FROM THE EDITOR: IBD drugs, 'liquid biopsies,' and DDW

The coming months will provide us welcome relief from health care politics as we turn our attention to the science of medicine. Digestive Disease Week® (DDW) will be in Washington, D.C. from June 2 to 5. Major themes already are emerging and implications for our clinical practices are exciting. In this month's issue of *GI & Hepatology News* we summarize a presentation about the IBD medication pipeline given by Dr. Bill Sandborn (UCSD) at the Crohn's & Colitis Congress™ (a partnership between the Crohn's & Colitis Foundation and AGA in Las Vegas). The number of medications that will enter clinical practice is impressive. Over the last several decades, we have defined multiple inflammatory pathways that can lead to IBD and developed medications that modify abnormal immune responses. We are entering an era of precision medicine never before seen in our specialty. Most of these biological medications can be given orally or subcutaneously, precluding the need for infusion centers. I anticipate an enormous offering of IBD-related science at DDW®.



DR. ALLEN

Two other articles this month should be read carefully. "Liquid biopsies" are coming. We know that solid cancers shed DNA into the circulation. We now have molecular tools to identify circulating tumor-related epigenetic and DNA changes at concentrations that are vanishingly low. These methodologies may allow screening for digestive cancers using blood and stool testing at accuracy rates that rival endoscopy – and at reduced cost. Other themes that we will see emphasized at DDW® include the microbiome, telehealth, precision health, and use of "big data" for predictive analysis and risk stratification of patients.

The Board of Editors appreciates the feedback that many of you sent us in our latest readership survey. Each month, we try hard to collect articles of clinical interest to the wide variety of clinicians and researchers that read *GI & Hepatology News*. We will continue to improve our offerings based on your valuable opinions.

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

DDSEP eight
Digestive Diseases Self-Education Program

Quick Quiz

Q1. A 37-year-old man with no significant past medical history presents with a dull, nonradiating epigastric pain for 3 months. The pain is not associated with eating or positional changes. He denies any heartburn, regurgitation, chest pain, nausea, vomiting, dysphagia, odynophagia, or weight loss. He currently does not take any medications. Family history is not significant. Physical examination reveals minimal tenderness to deep palpation in the epigastrum, but otherwise it is unremarkable. A complete blood count reveals a white blood cell count of 6, hemoglobin 10 g/dL, MCV 72 fL, and platelet count of 200 x 10^3/mcL.

What is the most important next step of management?
A. Schedule an abdominal ultrasound
B. Send an *H. pylori* stool antigen
C. Schedule an upper endoscopy
D. Empiric antisecretory therapy
E. Start amitriptyline 25 mg daily

Q2. A 68-year-old woman with alcoholic chronic pancreatitis has constant, disabling pain. She has previously tried gabapentin, celecoxib, and antioxidants with some improvement. She currently takes nonenteric coated pancrealipase (90,000 IU per meal) and controlled-release oxycontin. CT of the abdomen shows a few small punctate calcifications in the head of the pancreas, a 1-cm calculus in the genu with a markedly dilated pancreatic duct in the body and tail, and moderate distal atrophy. There are no pseudocysts. She discusses further options to treat her pain.

Which intervention will most likely improve her pain and quality of life over the next 5 years?
A. Continued medical therapy and increased dose of pancreatic enzymes
B. Lateral pancreaticojejunostomy (Peustow procedure)
C. ERCP with lithotripsy and stent placement
D. EUS-guided celiac plexus block
E. Total pancreatectomy with islet autotransplantation

The answers are on page 32.

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FRONTLINE MEDICAL COMMUNICATIONS

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FROM THE AGA JOURNALS

Engineered liver models to study human hepatotropic pathogens

BY CHHAVI JAIN
Frontline Medical News

Recently, exciting clinical progress has been made in the study of hepatotropic pathogens in the context of liver-dependent infectious diseases. Tissue engineering has been applied to authentically recapitulate human liver biology, facilitating the study of host-pathogen interactions during the entire pathogen life cycle. This is crucial for the development and validation of therapeutic interventions, such as drug and vaccine candidates that may act on the liver cells. The engineered models range from two-dimensional (2-D) cultures of primary human hepatocytes (HH) and stem cell–derived progeny to three-dimensional (3-D) organoid cultures and humanized rodent models. A review by Nil Gural and colleagues, published in Cellular and Molecular Gastroenterology and Hepatology (2018;5:131-44), described these unique models. Furthermore, the progress made in combining individual approaches and pairing the most appropriate model system and readout modality was discussed.

The major human hepatotropic pathogens include hepatitis C virus (HCV), hepatitis B virus (HBV), and the protozoan parasites *Plasmodium falciparum* and *P. vivax*. While HBV and HCV can cause chronic liver diseases such as cirrhosis and hepatocellular carcinoma, *Plasmodium* parasites cause malaria. The use of cancer cell lines and animal models to study host-pathogen interactions is limited by uncontrolled proliferation, abnormal liver-specific functions, and stringent host dependency of the hepatotropic pathogens. HHs are thus the only ideal system to study these pathogens, however, maintaining these cells ex vivo is challenging.

For instance, 2-D monolayers of human hepatoma-derived cell lines (such as HepG2-A16 and HepaRG) are easier to maintain, to amplify for scaling up, and to use for drug screening, thus representing a renewable alternative to primary hepatocytes. These model systems have been useful to study short-term infections of human *Plasmodium* parasites (*P. vivax* and *P. falciparum*); other hepatotropic pathogens such as Ebola, Lassa, human cytomegalovirus, and dengue viruses; and to generate virion stocks (HCV, HBV). For long-term scientific analyses and cultures, as well as clinical isolates of pathogens that do not infect hepatoma cells, immortalized cell lines have been engineered to differentiate and maintain HH functions for a longer duration. Additionally, cocultivation of primary hepatocytes with nonparenchymal cells or hepatocytes with mouse fibroblasts preserves hepatocyte phenotype. The latter is a self-assembling coculture system that could potentially maintain an infection for over 30 days and be used for testing anti-HBV drugs. A micropatterned coculture system, in which hepatocytes are positioned in "islands" via photolithographic patterning of collagen, surrounded by mouse embryonic fibroblasts, can maintain hepatocyte phenotypes for 4-6 weeks, and remain

Tissue engineering has been applied to authentically recapitulate human liver biology, facilitating the study of host-pathogen interactions during the entire pathogen life cycle.

Continued on following page

Gural et al. present a timely and outstanding review of the advances made in the engineering of human-relevant liver culture platforms for investigating the molecular mechanisms of infectious diseases (e.g., hepatitis B/C viruses and *Plasmodium* parasites that cause malaria) and developing better drugs or vaccines against such diseases. The authors cover a continuum of platforms with increasing physiological complexity, such as 2-D hepatocyte monocultures on collagen-coated plastic, 2-D cocultures of hepatocytes and nonparenchymal cells, (both randomly distributed and patterned into microdomains to optimize cell-cell contact), 3-D cultures/cocultures housed in biomaterial-based scaffolds, perfusion-based bioreactors to induce cell growth and phenotypic stability, and finally rodents with humanized livers. Cell sourcing considerations for building human-relevant platforms are discussed, including cancerous cell lines, primary human hepatocytes, and stem cell–derived hepatocytes (e.g., induced pluripotent stem cells).


DR. KHETANI

From the discussions of various studies, it is clear that this field has benefitted tremendously from advances in tissue engineering, including microfabrication tools adapted from the semiconductor industry, to construct human liver platforms that last for several weeks in vitro, can be infected with hepatitis B/C virus and *Plasmodium* parasites with high efficiencies, and are very useful for high-throughput and high-content drug screening applications. The latest protocols in isolating and cryopreserving primary human hepatocytes and differentiating stem cells into hepatocyte-like cells with adult functions help reduce the reliance on abnormal or cancerous cell lines for building platforms with higher relevance to the clinic. Ultimately, continued advances in microfabricated human liver platforms can aid our understanding of liver infections and spur further drug/vaccine development.

Salman R. Khetani, PhD, is associate professor, department of bioengineering, University of Illinois at Chicago. He has no conflicts of interest.

FROM THE AGA JOURNALS

Model supports endoscopic resection for some T1b esophageal adenocarcinomas

BY AMY KARON
Frontline Medical News

Endoscopic treatment of T1a esophageal adenocarcinoma outperformed esophagectomy across a range of ages and comorbidity levels in a Markov model.

Esophagectomy produced 0.16 more unadjusted life-years, but led to 0.27 fewer quality-adjusted life-years (QALYs), in the hypothetical case of a 75-year-old man with T1aN0M0 esophageal adenocarcinoma (EAC) and a Charlson comorbidity index score of 0, reported Jacqueline N. Chu, MD, of Massachusetts General Hospital, Boston, and her associates. "[We] believe QALYs are a more important endpoint because of the significant morbidity associated with esophagectomy," they wrote in the March issue of Clinical Gastroenterology and Hepatology.

In contrast, the model portrayed the management of T1b EAC as "an individualized decision" – esophagectomy was preferable in 60- to 70-year-old patients with T1b EAC, but serial endoscopic treatment was better when patients were older, with more comorbidities, the researchers said. "For the sickest patients, those aged 80 and older with comorbidity index of 2, endoscopic treatment not only provided more QALYs but more unadjusted life years as well."

Treatment of T1a EAC is transitioning from esophagectomy to serial endoscopic resection, which physicians still tend to regard as too risky in T1b EAC. The Markov model evaluated the efficacy and cost efficacy of the two approaches in hypothetical T1a and T1b patients of various ages and comorbidities, using cancer death data from the Surveillance, Epidemiology, and End Results (SEER) Medicare database and published cost data converted to 2017 U.S. dollars based on the U.S. Bureau of Labor Statistics' Consumer Price Index.

Like the T1a case, the T1b base case consisted of a 75-year-old man with a Charlson comorbidity index of 0. Esophagectomy produced 0.72 more unadjusted life years than did endoscopic treatment (5.73 vs. 5.01) while yielding 0.22 more QALYs (4.07 vs. 3.85, respectively). Esophagectomy cost $156,981 more, but the model did not account for costs of chemotherapy and radiation or palliative care, all of which are more likely with endoscopic resection than esophagectomy, the researchers noted.

In sensitivity analyses, endoscopic treatment optimized quality of life in T1b EAC patients who were older than 80 years and had a comorbidity index of 1 or 2. Beyond that, treatment choice depended on posttreatment variables. "[If] a patient considered his or her quality of life postesophagectomy nearly equal to, or preferable to, [that] postendoscopic treatment, esophagectomy would be the optimal treatment strategy," the investigators wrote. "An example would be the patient who would rather have an esophagectomy than worry about recurrence with endoscopic treatment."

Pathologic analysis of T1a EACs can be inconsistent, and the model did not test whether high versus low pathologic risk affected treatment preference, the researchers said. They added data on T1NOS (T1 not otherwise specified) EACs to the model because the SEER-Medicare database included so few T1b endoscopic cases, but T1NOS patients had the worst outcomes and were in fact probably higher stage than T1. Fully 31% of endoscopy patients were T1NOS, compared with only 11% of esophagectomy patients, which would have biased the model against endoscopic treatment, according to the investigators.

'[If] a patient considered his or her quality of life postesophagectomy nearly equal to, or preferable to, [that] postendoscopic treatment, esophagectomy would be the optimal treatment strategy,' the investigators wrote.

The National Institutes of Health provided funding. Dr. Chu reported having no conflicts of interest. Three coinvestigators disclosed ties to CSA Medical, Ninepoint, C2 Therapeutics, Medtronic, and Trio Medicines. The remaining coinvestigators had no conflicts.

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SOURCE: Chu JN et al. Clin Gastroenterol Hepatol. 2017 Nov 24. doi: 10.1016/j.cgh.2017.10.024.

Continued from previous page

permissive to *P. falciparum*, *P. vivax*, HBV, and HCV infections. Furthermore, micropatterned coculture systems support full developmental liver stages of both *P. falciparum* and *P. vivax*, with the release of merozoites from hepatocytes and their subsequent infection of overlaid human red blood cells.

Alternatively, embryonic stem cells and induced pluripotent stem cells of human origin can be differentiated into hepatocytelike cells that enable investigation of host genetics within the context of host-pathogen interactions, and can also be used for target identification for drug development. However, stem cell cultures require significant culture expertise and may not represent a fully differentiated adult hepatocyte phenotype.

Although 2-D cultures offer ease of use and monitoring of infection, they often lack the complexity of the liver microenvironment and impact of different cell types on liver infections. A 3-D radial-flow bioreactor (cylindrical matrix) was able to maintain and amplify human hepatoma cells (for example, Huh7 cells), by providing sufficient oxygen and nutrient supply, supporting productive HCV infection for months. Other 3-D cultures of hepatoma cells using polyethylene glycol–based hydrogels, thermoreversible gelatin polymers, alginate, galactosylated cellulosic sponges, matrigel, and collagen have been developed and shown to be permissive to HCV or HBV infections. Although 3-D coculture systems exhibit better hepatic function and differential gene expression profiles in comparison to 2-D counterparts, they require a large quantity of cells and are a challenge to scale up. Recently, several liver-on-a-chip models have been created that mimic shear stress, blood flow, and the extracellular environment within a tissue, holding great potential for modeling liver-specific pathogens.

Recently, several liver-on-a-chip models have been created that mimic shear stress, blood flow, and the extracellular environment within a tissue.

Humanized mouse models with ectopic human liver structures have been developed in which primary HHs are transplanted following liver injury. Chimeric mouse models including Alb-uPA/SCID (HHs transplanted into urokinase-type plasminogen activator-transgenic severe combined immunodeficient mice), FNRG/FRG (HHs transplanted into Fah[-/-], Rag2[-/-], and Il2rg[-/-] mice with or without a nonobese diabetic background), and TK-NOG (HHs transplanted into herpes simplex virus type-1 thymidine kinase mice) were validated for HCV, HBV, *P. falciparum*, and *P. vivax* infections. It is, however, laborious to create and maintain chimeric mouse models and monitor infection processes in them.

It is important to note that the selection of model system and the readout modality to monitor infection will vary based on the experimental question at hand. Tissue engineering has thus far made significant contributions to the knowledge of hepatotropic pathogens; a continued effort to develop better liver models is envisioned.

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SOURCE: Gural N et al. Cell Mol Gastronterol Hepatol. 2018;5:131-44.).

FROM THE AGA JOURNALS

Sofosbuvir/ledipasvir safe in HBV coinfected patients

BY AMY KARON
Frontline Medical News

For patients with chronic hepatitis C and hepatitis B virus (HBV) coinfection, 12 weeks of ledipasvir/sofosbuvir therapy achieved a 100% sustained viral response rate without causing liver failure or death in a phase 3b, multicenter, open-label study.

"Although we observed increases in HBV DNA in most patients, these increases were [usually] not associated with ALT [alanine amino transferase] flares or clinical complications," reported Chun-Jen Liu, MD, of National Taiwan University College of Medicine and Hospital, Taipei, and his associates. Although nearly two-thirds of patients developed HBV reactivation, less than 5% developed alanine aminotransferase rises at least twice the upper limit of normal, and only one patient had symptomatic HBV reactivation, which entecavir therapy resolved. This study was the first to prospectively evaluate the risk of HBV reactivation during HCV treatment, the researchers wrote in the March issue of Gastroenterology.

Because chronic hepatitis C virus infection tends to suppress HBV replication, peginterferon/ribavirin or direct-acting anti-HCV treatment can reactivate HBV infection, especially in patients who test positive for hepatitis B surface antigen (HBsAg). Left untreated, reactivated HBV can lead to fulminant hepatitis, liver failure, and death, as noted on recently mandated boxed warnings.

Accordingly, guidelines recommend testing patients for HBV infection before starting HCV treatment.

The study enrolled 111 coinfected patients; about two-thirds were female, and 16% had compensated cirrhosis. All tested positive for HBsAg at screening, and all but one also tested positive at baseline. Mean baseline HBV DNA levels were 2.1 $\log_{10}$ IU/mL. Patients received 90 mg ledipasvir plus 400 mg sofosbuvir for 12 weeks, and levels of HCV RNA, HBV DNA, and HBsAg were tested at weeks 1, 2, 4, 8, 12, posttreatment week 4, and then every 12 weeks until posttreatment week 108.

In all, 70 (63%) patients developed HBV reactivation, including 84% of the 37 patients with undetectable HBV DNA at baseline. During treatment, none of these patients had ALT rise more than twice the upper limit of normal. By 48 weeks post treatment, however, 77% still had quantifiable HBV DNA, and two had marked ALT rises. Furthermore, by posttreatment week 53, one of these patients developed bilirubinemia and symptomatic HBV infection (malaise, anorexia, sclera jaundice, and nausea), which resolved after treatment with entecavir.

A total of 74 patients had quantifiable baseline HBV DNA (at least 20 IU/mL). Three received entecavir or tenofovir disoproxil fumarate based on confirmed HBV reactivation with a concomitant ALT rise of at least twice the upper limit of normal. All were asymptomatic. There were no cases of liver failure or death.

"Regardless of HBV DNA and/or ALT elevations, no patient had signs of liver failure," the researchers wrote. "Our results support the recommendations put forth in clinical treatment guidelines: HCV-infected patients should be evaluated for HBV infection prior to HCV treatment with direct-acting antivirals. Those who are HBsAg positive should be monitored during and after treatment for HBV reactivation, and treatment should be initiated in accordance with existing guidelines."

Gilead funded the study. Dr. Liu and 12 coinvestigators reported having no conflicts of interest. Nine coinvestigators reported being employees and shareholders of Gilead, and one coinvestigator reporting consulting for Gilead. The senior author disclosed ties to Roche, Bristol-Myers Squibb, Johnson & Johnson, Bayer, MSD, and Taiha.

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SOURCE: Liu C-J et al. Gastroenterology. 2017 Nov 21. doi: 10.1053/j.gastro.2017.11.011.

Ulcerative colitis is disabling over time

BY AMY KARON
Frontline Medical News

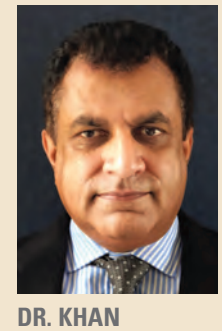
Between 70% and 80% of patients with ulcerative colitis relapsed within 10 years of diagnosis and 10%-15% had aggressive disease in a meta-analysis of 17 population-based cohorts spanning 1935 to 2016.

However, "contemporary population-based cohorts of patients diagnosed in the biologic era are lacking," [and they] "may inform us of the population-level impact of paradigm shifts in approach to ulcerative colitis management during the last decade, such as early use of disease-modifying biologic therapy and treat-to-target [strategies]," wrote Mathurin Fumery, MD, of the University of California, San Diego. The report was published in the March issue of Clinical Gastroenterology and Hepatology.

Population-based observational cohort studies follow an entire group in a geographic area over an extended time, which better characterizes the true natural history of disease outside highly controlled settings of clinical trials, the reviewers noted. They searched MEDLINE for population-based longitudinal studies of adults with newly diagnosed ulcerative colitis, whose medical records were reviewed, and who were followed for at least a year. They identified 60 such studies of 17 cohorts that included 15,316 patients in southern and northern Europe, Australia, Israel, the United States, Canada, China, Hong Kong,

Continued on following page

Understanding the natural history of ulcerative colitis (UC) is imperative especially in view of emerging therapies that could have the potential to alter the natural course of disease. Dr. Fumery and his colleagues are to be congratulated for conducting a comprehensive review of different inception cohorts across the world and evaluating different facets of the disease. They found that the majority of patients had a mild-moderate disease course, which was most active at the time of diagnosis. Approximately half the patients require UC-related hospitalization at some time during the course of their disease. Similarly, 50% of patients received corticosteroids, and while almost all patients with UC were treated with mesalamine within 1 year of diagnosis, 30%-40% are not on mesalamine long term. They also identified consistent predictors of poor prognosis, including young age at diagnosis, extensive disease, early need for corticosteroids, and elevated biochemical markers.



DR. KHAN

These results are reassuring because they reinforce the previous observations that roughly half the patients with UC have an uncomplicated disease course and that the first few years of disease are the most aggressive. A good indicator was that the proportion of patients receiving corticosteroids decreased over time. The disheartening news was that the long-term colectomy rates have generally remained stable over time.

The surprising aspect was the scarcity of data from North America; almost half the studies were from Scandinavian countries. There was also limited information on the impact of biologics and future research must be undertaken to evaluate their effect on the natural history of disease – especially the impact of early introduction among those who have poor prognostic features. This will go a long way in developing a personalized medicine approach in the management of UC.

Nabeel Khan, MD, is assistant professor of clinical medicine, University of Pennsylvania, Philadelphia, and director of gastroenterology, Philadelphia Veterans Affairs Medical Center. He has received research grants from Takeda, Luitpold, and Pfizer.

FROM THE AGA JOURNALS

No short-term link found between PPIs, MI

BY AMY KARON
Frontline Medical News

Starting a prescription proton pump inhibitor (PPI) conferred no short-term increase in risk for myocardial infarction in a large retrospective insurance claims study.

Over a median follow-up of 2-3 months, estimated weighted risks of first-ever MI were low and similar regardless of whether patients started PPIs or histamine$_2$-receptor antagonists (H2RAs), reported Suzanne N. Landi of the University of North Carolina at Chapel Hill, and her associates. "Contrary to prior literature, our analyses do not indicate increased risk of MI in PPI initiators compared to histamine$_2$-receptor antagonist initiators," they wrote in the March issue of Gastroenterology.

Epidemiologic studies have produced mixed findings on PPI use and MI risk. Animal models and ex vivo studies of human tissue indicate that PPIs might harm coronary vessels by increasing plasma levels of asymmetrical dimethylarginine, which counteracts the vasoprotective activity of endothelial nitrous oxide synthase, the investigators noted.

To further assess PPIs and risk of MI while minimizing potential confounding, they studied new users of either prescription PPIs or an active comparator, prescription H2RAs. The dataset included administrative claims for more than 5 million patients with no MI history who were enrolled in commercial insurance plans or Medicare Supplemental Insurance plans. The study data spanned from 2001 to 2014, and patients were followed from their initial antacid prescription until they either developed a first-ever MI, stopped their medication, or left their insurance plan. Median follow-up times were 60 days in patients with commercial insurance and 96 days in patients with Medicare Supplemental Insurance, which employers provide for individuals who are at least 65 years old.

After controlling for numerous measurable clinical and demographic confounders, the estimated 12-month risk of MI was about 2 cases per 1,000 commercially insured patients and about 8 cases per 1,000 Medicare Supplemental Insurance enrollees. The estimated 12-month risk of MI did not significantly differ between users of PPIs and H2RAs, regardless of whether they were enrolled in commercial insurance plans (weighted risk difference per 1,000 users, –0.08; 95% confidence interval, –0.51 to 0.36) or Medicare Supplemental Insurance (weighted risk difference per 1,000 users, –0.45; 95% CI, –1.53 to 0.58) plans.

Each antacid class also conferred a similar estimated risk of MI at 36 months, with weighted risk differences of 0.44 (95% CI, –0.90 to 1.63) per 1,000 commercial plan enrollees and –0.33 (95% CI, –4.40 to 3.46) per 1,000 Medicare Supplemental Insurance plan enrollees, the researchers reported. Weighted estimated risk ratios also were similar between drug classes, ranging from 0.87 (95% CI, 0.76 to 0.99) at 3 months among Medicare Supplemental Insurance enrollees to 1.08 (95% CI, 0.87 to 1.35) at 36 months among commercial insurance plan members.

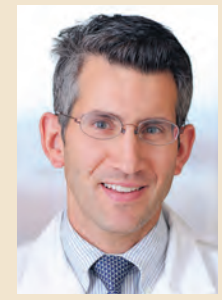
"Previous studies have examined the risk of MI in PPI users and compared directly to nonusers, which may have resulted in stronger confounding by indication and other risk factors, such as BMI [body mass index] and baseline cardiovascular disease," the investigators wrote. "Physicians and patients should not avoid starting a PPI because of concerns related to MI risk."

The researchers received no grant support for this study. Ms. Landi disclosed a student fellowship from UCB Biosciences.

ginews@gastro.org

SOURCE: Landi SN et al. Gastroenterology. 2017 Nov 6. doi: 10.1053/j.gastro.2017.10.042.

In the late 2000s, several large epidemiologic studies suggested that proton pump inhibitors (PPIs) increase the risk for MI in users of clopidogrel. There was a proposed mechanism: PPIs competitively inhibit cytochrome P450 isoenzymes, which blocked clopidogrel activation and, ex vivo, increased platelet aggregation. It sounded scary – but fortunately, some reassuring data quickly emerged. In 2007, the COGENT trial randomized patients with cardiovascular disease to a PPI/clopidogrel versus a placebo/clopidogrel combination pill. After 3 years of follow-up, there was no difference in rates of death or cardiovascular events. In the glaring light of this randomized controlled trial data, earlier studies didn't look so convincing.


DR. FREEDBERG

So why won't the PPI/MI issue die? In part because COGENT was a relatively small study. It included 3,761 patients, but the main result depended on 109 cardiovascular events. Naysayers have argued that perhaps if COGENT had been a bigger study, the result would have been different.

In this context, the epidemiologic study by Suzanne Landi and her associates provides further reassurance that PPIs do not cause MI. Two insurance cohorts comprising over 5 million patients were used to compare PPI users with histamine$_2$-receptor antagonist users after adjusting for baseline differences between the two groups. The large size of the dataset allowed the authors to make precise estimates; we can say with confidence that there was no clinically relevant PPI/MI risk in these data.

Can we forget about PPIs and MI? These days, my patients worry more about dementia or chronic kidney disease. But the PPI/MI story is worth remembering. Large epidemiologic studies are sometimes contradicted by subsequent studies and need to be evaluated in context.

Daniel E. Freedberg, MD, MS, is an assistant professor of medicine at the Columbia University Medical Center, New York. He has consulted for Pfizer.

Continued from previous page

Indonesia, Macau, Malaysia, Singapore, Sri Lanka, and Thailand.

Left-sided colitis was most common (median, 40%; interquartile range, 33%-45%) and about 10%-30% of patients had disease extension. Patients tended to have mild to moderate disease that was most active at diagnosis and subsequently alternated between remission and mild activity. However, nearly half of patients were hospitalized at some point because of ulcerative colitis, and about half of that subgroup was rehospitalized within 5 years. Furthermore, up to 15% of patients with ulcerative colitis underwent colectomy within 10 years, a risk that mucosal healing helped mitigate. Use of corticosteroids dropped over time as the prevalence of immunomodulators and anti–tumor necrosis factor therapy rose.

"Although ulcerative colitis is not associated with an increased risk of mortality, it is associated with high morbidity and work disability, comparable to Crohn's disease," the reviewers concluded. Not only are contemporary population-level data lacking, but it also remains unclear whether treating patients with ulcerative colitis according to baseline risk affects the disease course, or whether the natural history of this disease differs in newly industrialized nations or the Asia-Oceania region, they added.

Dr. Fumery disclosed support from the French Society of Gastroenterology, AbbVie, MSD, Takeda, and Ferring. Coinvestigators disclosed ties to numerous pharmaceutical companies.

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SOURCE: Fumery M et al. Clin Gastroenterol Hepatol. 2017 Jun 16. doi: 10.1016/j.cgh.2017.06.016.

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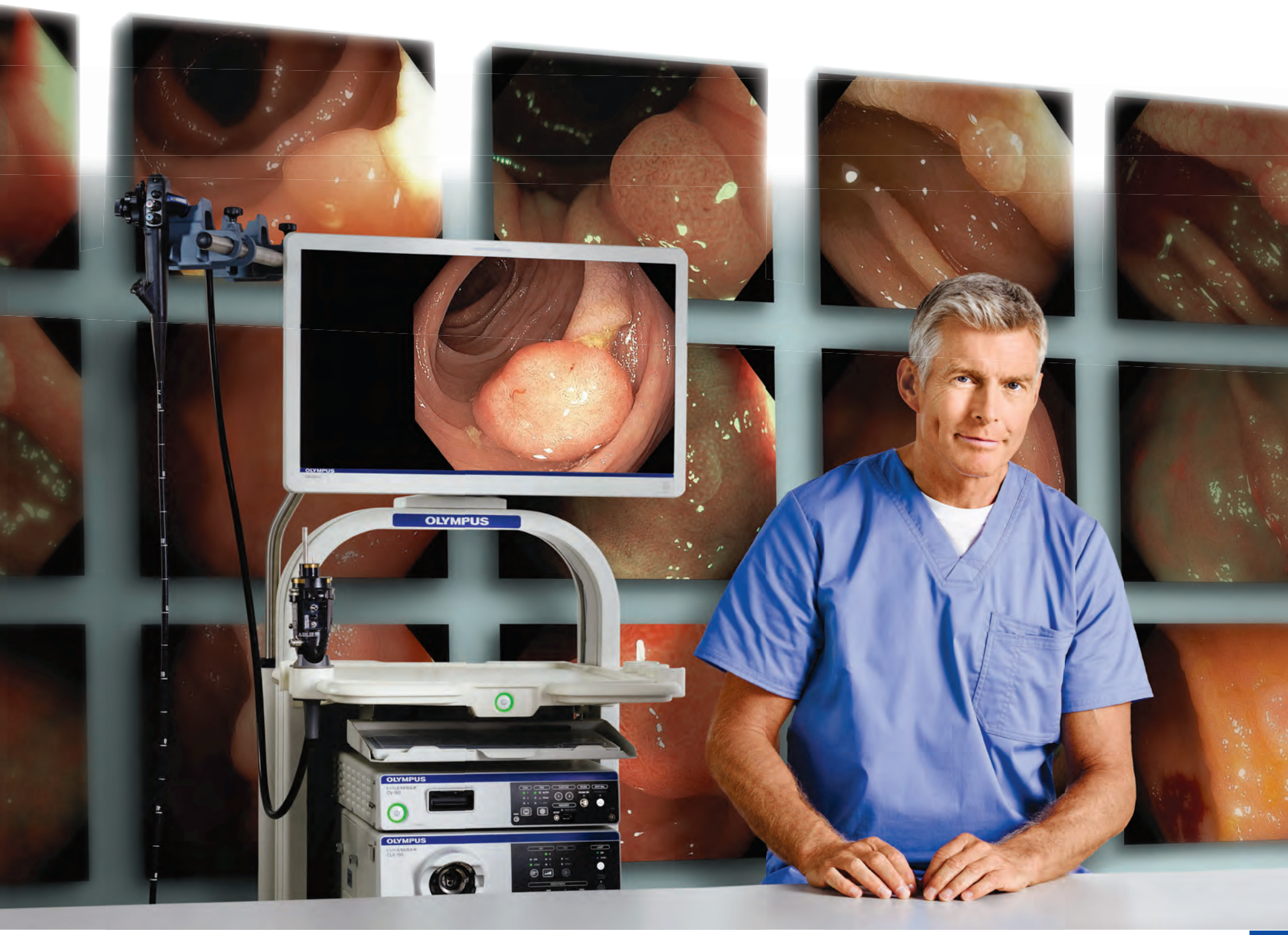

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AGA's FMT National Registry enrolls first patient

The AGA Fecal Microbiota Transplantation (FMT) National Registry is officially underway! The first patient enrolled in the FMT National Registry received a fecal transplant through the Gastroenterology Center of Connecticut/Medical Research Center of Connecticut by Paul Feuerstadt, MD. The patient being treated had experienced multiple recurrences of *C. difficile* infection. As part of the registry, Dr. Feuerstadt will follow up with the patient four times over the next 2 years and report back on the patient's health post-FMT. The patient will also provide yearly reports for up to 10 years.

The AGA FMT National Registry, a program of the AGA Center for Gut Microbiome Research and Education, was established in August 2016 after receiving funding from the National Institute of Allergy and Infectious Diseases (NIAID) of the NIH (award number R24AI118629). The registry aims to enroll 75 sites and track 4,000 patients for 5-10 years after their FMT procedure. The data collected from this registry will guide physicians in determining when to use FMT on their patients and will provide much-needed information on the potential risks associated with stool transplants.

If you're interested in participating in the registry, email FMTRegistry@gastro.org.

As part of the registry, Dr. Feuerstadt will follow up with the patient four times over the next 2 years and report back on the patient's health.

New registry collaborators

AGA will collaborate with the American Gut Project – an academic effort run by the laboratory of Rob Knight, PhD, professor and director of the Center for Microbiome Innovation at the University of California, San Diego – to build a biobank of stool samples from participants in the FMT National Registry. American Gut will receive stool samples from registry participants before and after their FMT. The microbiota will be sequenced in each sample, and remaining material will be frozen to be made available for future research. Eventually, this information could help doctors screen and select the best donor samples for individual patients.

AGA will also collaborate with OpenBiome, a public stool bank and nonprofit research organization that provides clinicians with rigorously screened, ready-to-use stool preparations for fecal transplant procedures. As the only public stool bank in the country, OpenBiome serves as the source of stool preparations for nearly 1,000 clinical partners performing FMT across the U.S. For patients enrolled in the registry who receive OpenBiome FMT material, OpenBiome will provide screening information and samples to support the registry's research analyses. Learn more at www.gastro.org/FMTRegistry.

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DDW® 2018 general registration is now open

General registration and housing for Digestive Disease Week® (DDW) 2018 are now open. Registering during the early-bird period (until April 18) guarantees a savings of at least $80 on your registration.

Why DDW?

Just as monumental as this year's host city, Washington, D.C., DDW is the premier meeting for GI professionals. Come to DDW 2018, taking place June 2-5, to:

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- Explore research unveiled in more than 4,000 poster presentations and over 1,000 abstract presentations.
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Headlines from the 2018 Gastrointestinal Cancers Symposium

The 2018 Gastrointestinal Cancers Symposium took place Jan. 18-20, 2018, in San Francisco. During the meeting, investigators presented groundbreaking research designed to improve the diagnosis and treatment of gastrointestinal cancers. Here are some of the most noteworthy headlines from the 2018 meeting.

Promising Results Using Liquid Biopsy to Improve CRC Early Detection

Researchers in Taiwan developed a screening test for early colorectal cancer (CRC) detection that requires a simple blood draw to assess for circulating tumor cells in the blood. The test demonstrates 88% accuracy to detect all stages of colorectal illness, including precancerous lesions. If validated and made commercially available, this test could be readily integrated into a patient's routine physical exam, thereby increasing CRC screening compliance.

CELESTIAL Results May Lead to Cabozantinib Approval in Second-Line HCC

The phase III CELESTIAL trial met its primary endpoint by demonstrating a survival advantage with cabozantinib in patients with advanced hepatocellular carcinoma (HCC) that progressed following prior systemic therapy. Other outcomes included improvements in progression-free survival and objective response rate, as well as an acceptable safety profile, thus positioning cabozantinib for potential approval in the second-line setting in HCC.

RAINFALL Meets Primary Endpoint, But Ramucirumab Will Not Be Pursued for a First-Line Indication in G-GEJ Cancer

Results of the global, randomized, double-blind, placebo-controlled, phase III RAINFALL trial established the statistical benefit of ramucirumab, a monoclonal antibody targeting VEGFR-2, added to standard chemotherapy for patients with previously untreated metastatic gastric or gastroesophageal junction (G-GEJ) adenocarcinoma. The findings revealed a significant 25% reduction in the risk of disease progression or death for the primary endpoint of progression-free survival (PFS). However, the reduction corresponded to only a 9-day improvement in median PFS, so the clinical benefit of frontline ramucirumab is debatable.

The Gastrointestinal Cancers Symposium is cosponsored by AGA, the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO) and the Society of Surgical Oncology (SSO).

More news from the 2018 Gastrointestinal Cancers Symposium is available at gicasym.org/daily-news.

ginews@gastro.org

Thank you to our top Community contributors

2017 was a busy year in the AGA Community, our member-only discussion forum. Some of our favorite discussions included challenging clinical cases you shared, remembering your colleague Dr. Marv Sleisenger and first-hand recaps of AGA's Advocacy Day experiences.

Thank you to everyone who contributed to the conversations in 2017, making the AGA Community a hub for collaboration to ever-expand the field of GI.

Tied for the title of top contributor in 2017 were Dmitriy Kedrin, MD, PhD, of Elliot Hospital in Manchester, N.H., and Sunanda Kane, MD, MSPH, AGAF, of Mayo Clinic in Rochester, MN.

Both are key influencers in the forum, especially with helping colleagues manage challenging patient cases. Learn more about each contributor and why keeping up with the Community is an important part of their regular routines in this brief Q&A.

Thanks for being such an active member of the AGA Community! Why do you contribute?

Dr. Kane: "You are welcome! I contribute because I feel I have helpful suggestions and recommendations for managing difficult patient scenarios as well as for professional issues."

Dr. Kedrin: "I think it is important for GI docs to be a part of a larger community, stay informed on latest guidelines, research publications and approaches to difficult cases, where more than one road can be taken. I feel that it is a great forum for someone like me, relatively junior gastroenterologist."

Why do you enjoy being part of the AGA Community?

Kane: "I feel engaged with my colleagues who I otherwise do not see on a regular basis, and get to 'meet' new ones."

Kedrin: "I find the case discussions informative. I learn a great deal about current trends and opinions on important topics in the GI world."

What do you like to do in your free time?

Kane: "I enjoy cooking and binge-watching Netflix."

Kedrin: "I bake bread and run a gastroenterology literature review podcast called 'GI Pearls.'"

What's your approach to handling a difficult patient case you come across in your practice?

Kane: "I reach out to as many of my colleagues as I think appropriate who may have some experience or thoughts about how to help a difficult patient."

Kedrin: "I often seek advice of other clinicians, some with more expertise in a particular area. I also go to the literature and try to learn more that way, help expand my differential as well as figure out the best therapeutic approach."

Was there a conversation in the AGA Community in 2017 that was your favorite?

Kane: "All conversations have merit, none stick out as a favorite."

Kedrin: "Oh, there are several. I recall a patient case where there were several thought leaders in the field who had a disagreement about the best approach to treatment. The work-life balance conversation [Early Career Group members only] was also very good. I also enjoyed reading about different opinions regarding the values of randomized versus observational trials that happened a while back."

View the top discussions and contributors from 2017 on the AGA Community homepage, for a limited time.

ginews@gastro.org

AGA Pres. Sheila Crowe spends the day on Capitol Hill

AGA President Sheila Crowe, MD, FRCPC, FACP, FACG, AGAF, recently spent the day on Capitol Hill meeting with lawmakers to advocate for AGA legislative priorities including increasing funding for NIH and biomedical research, support for the Removing Barriers to Colorectal Cancer Screening Act, and support for the Restoring the Patient's Voice Act. Dr. Crowe met with eight congressional offices and received helpful feedback on the upcoming agenda in Congress and how it impacts AGA's priorities.

NIH funding

Dr. Crowe stressed the need for increased funding for NIH and biomedical research, making the case that funding NIH not only improves the quality of life for Americans, but also contributes to our nation's economic competitiveness. Fortunately, the offices that we met with were very supportive of increasing NIH funding, including the offices of House and Senate Appropriations Subcommittee Chairs Tom Cole, R-OK, and Roy Blunt, R-MO, who have worked in a bicameral fashion to increase funding for NIH. Both offices were confident that leadership was close to a deal to increase the current budget caps, which would enable increased funding for NIH.

Removing Barriers to Colorectal Cancer Screening Act

Fixing the current coinsurance problem for Medicare beneficiaries who undergo a screening colonoscopy that becomes therapeutic remains a top AGA priority. Most of the offices that Dr. Crowe met with were cosponsors of the legislation, the Removing Barriers to Colorectal Cancer Screening Act (HR 1017/S.479), that would waive coinsurance payment regardless of the screening outcome. Dr. Crowe shared her experience with patients and the financial burden this places on beneficiaries who need to be screened. Rep. Raul Ruiz, D-CA, and Rep. Scott Peters, D-CA, both members of the House Energy and Commerce Committee and supporters of the bill, will continue to advocate that the bill receive a hearing this year to help move it through Congress. The bill continues to have wide bipartisan support. Read more about the issue and how you can explain it to your patients.

Step therapy

More and more patients are being subject to step therapy protocols, also known as "fail first" under which they are required to try and fail sometimes two or three therapies before receiving coverage of the initial therapy recommended by their physician. With the emergence of new biologics to treat diseases like inflammatory bowel disease, more and more digestive disease patients are being subject to these protocols, which can

Dr. Sheila Crowe lobbied for AGA priorities on Capitol Hill.

have adverse effects on their health. Restoring the Patient's Voice Act (HR 2077) would provide patients and providers with a fair and equitable appeals process when step therapy has been imposed and provides common sense exceptions for the provider to appeal. Dr. Crowe spoke of the impact this policy is having on digestive disease patients and the burden it puts on physician practices that have to take time away from patients to navigate the convoluted insurance appeals process. We are hopeful that many of the offices that we met with will support HR 2077. Read more about the issue.

Food is Medicine Working Group

Dr. Crowe also had a productive meeting with Rep. Jim McGovern's, D-MA, office and learned more about the recently created Food is Medicine Working Group that he has initiated. McGovern is the Ranking Member of the Agriculture Committee's Subcommittee on Nutrition which is responsible for our nation's nutrition guidelines and the Supplemental Nutrition Assistance Program. The Working Group will focus on costs related to hunger and the importance of nutrition in treating chronic illness and disease. AGA looks forward to working with McGovern and members of the Working Group on this bipartisan initiative.

Capitol Hill needs to hear the voice of GI

In conjunction with Dr. Crowe's visit, AGA launched a Virtual Advocacy Day to encourage members to contact their legislators in support of the issues that Dr. Crowe was advocating during her meetings. We thank those members who took time out of their schedules to take action.

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Legacy Society members sustain research

AGA Legacy Society members share a desire to guarantee long-term support for digestive disease research. Through their foresight and generosity, they help ensure the continued momentum of discovery that has characterized GI medicine in recent decades. Legacy Society member donations directly support young GI investigators as they establish independent research careers.

Legacy Society members are the most generous individual donors to the AGA Research Foundation. Members of the AGA Legacy Society provide tax-deductible gifts to the AGA Research Foundation of $5,000 or more per year for 5 years ($25,000 total) or $50,000 or more in a planned gift, such as a bequest. All Legacy Society contributions go directly to support research awards.

AGA members support young researchers at a critical decision point in their lives – when many consider giving up their research careers due to a lack of funding. "I am honored to be a recipient of the Research Scholar Award. I would like to thank the foundation for their generous contribution that will fund a crucial transition in my career," said Jose Saenz, MD, PhD, Washington University School of Medicine and 2017 AGA – Gastric Cancer Foundation Research Scholar Award recipient.

The AGA Research Foundation's mission is to raise funds to support young researchers in gastroenterology and hepatology. Gifts to the foundation support researchers who are working to advance our understanding of digestive diseases.

"I am extremely grateful to be selected for this award. I would like to thank the foundation donors for their generous support. This award will me build a research program to better understand mechanisms that promote growth of cholangiocarcinoma," remarks Silvia Affo, PhD, Columbia University, 2017 AGA Research Scholar recipient.

Donors who make gifts at the Legacy Society level before DDW will receive an invitation to the annual Benefactors' Dinner at the Folger Shakespeare Library in Washington, DC. Individuals interested in learning more about Legacy Society membership may contact Stacey Hinton Tuneski, Senior Director of Development at stuneski@gastro.org or via phone (301) 222-4005. More information on the AGA Legacy Society including the current roster and acceptance form is available on the foundation's website at www.gastro.org/legacysociety.

ginews@gastro.org

The makings of a grand celebration

Beginning with a memorable gathering at the United States Library of Congress in 2007, the AGA Benefactors' Dinner has welcomed members of the AGA Legacy Society and other AGA dignitaries to special locations nationwide. The Folger Shakespeare Library will be the location of the 2018 AGA Research Foundation Benefactors' Dinner during DDW in Washington, DC. Just steps from the Capitol, the Great Hall and Pastor Reading room are a spectacular setting for an enjoyable evening with friends.


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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Multiple targets for new drugs

Pipeline *from page 1*

ous etrolizumab (100 mg at weeks 0, 4, and 8, with placebo at week 2 or a 420-mg loading dose at week 0 followed by 300 mg at weeks 2, 4, and 8), or matching placebo (The Lancet 2014 348;309-18). They found that etrolizumab was more likely to lead to clinical remission at week 10 than was placebo, especially at the 100-mg dose. Meanwhile, a more recent study of the anti-MadCAM antibody PF-00547659 in patients with moderate to severe ulcerative colitis found that it was better than placebo for induction of remission (The Lancet 2017;390:135-44). Investigators for the trial, known as TURANDOT, found that the greatest clinical effects were observed with the 22.5-mg and 75-mg doses. "This is now being taken forward in phase 3 trials by Shire," Dr. Sandborn said.

The anti-interleukin 12/23 antibody (p40) ustekinumab is being investigated for efficacy in UC, while anti-interleukin 23 (p19) antibodies being studied include brazikumab (MEDI2070), risankizumab (BI-655066), geslekumab, mirikizumab (LY3074828), and tildrakizumab (MK-3222). In 2015, Janssen launched NCT02407236, with the aim of evaluating the effectiveness and safety of continuing ustekinumab as a subcutaneous (injection) maintenance therapy in patients with moderately to severely active UC who have demonstrated a clinical response to an induction treatment with intravenous ustekinumab. The estimated primary completion date is April 12, 2018. Meanwhile, a phase 2a trial of 119 patients with moderate to severe Crohn's disease who had failed treatment with tumor necrosis factor (TNF) antagonists showed that treatment with MEDI2070 was associated with clinical improvement after 8 and 24 weeks of therapy (Gastroenterol 2017;153:77-86). The investigators also found that patients with baseline serum IL-22 concentrations above the median threshold concentration of 15.6 pg/mL treated with MEDI2070 had higher rates of clinical response and remission, compared with those with baseline concentrations below this threshold. According to Dr. Sandborn, who was not involved in the study, these results provide support for further research on the value of IL-22 serum concentrations to predict response to MEDI2070. "It's a small study and is hypothesis generating," he said. "This will need to be confirmed in subsequent trials."

In a short-term study of 121 patients with active Crohn's disease, Brian G. Feagan, MD, Dr. Sandborn, and associates found that risankizumab was more effective than placebo for inducing clinical remission, particularly at the 600-mg dose, compared with the 200-mg dose (Lancet 2017;389:1699-709). The researchers also observed significant differences in endoscopic remission among patients on the study drug, compared with those on placebo (17% vs. 3%; $P = .0015$) as well as endoscopic response (32% vs. 13%; $P = .0104$). The trial provides further evidence that selective blockade of interleukin 23 via inhibition of p19 might be a viable therapeutic approach in Crohn's disease.

Dr. William J. Sandborn

Janus kinase (JAK) inhibitors under investigation for Crohn's disease include tofacitinib, filgotinib, upadacitinib, baricitinib, and TD-1473. In the OCTAVE Induction 1 trial led by Dr. Sandborn, 18.5% of the patients in the tofacitinib group achieved remission at 8 weeks, compared with 8.2% in the placebo group ($P = .007$); in the OCTAVE Induction 2 trial, remission occurred in 16.6% vs. 3.6% (P less than .001). In the OCTAVE Sustain trial, remission at 52 weeks occurred in 34.3% of the patients in the 5-mg tofacitinib group and 40.6% in the 10-mg tofacitinib group vs. 11.1% in the placebo group (P less than 0.001 for both comparisons with placebo; N Engl J Med. 2017;376:1723-36). "In subgroup analyses, it looks like the 10-mg dose is more effective for maintenance in patients who previously received anti-TNF therapy," said Dr. Sandborn, who also directs the UCSD IBD Center. "All secondary outcomes were positive. You don't see that very often. It tells you that this is a really effective therapy. It's currently being reviewed by the FDA."

Meanwhile, a phase 2 trial found that a higher percentage of patients with mild to moderate Crohn's disease who received a 200-mg dose of filgotinib over 10 weeks achieved clinical remission, compared with those who received placebo (47% vs. 23%, respectively; $P = .0077$; The Lancet 2017;389:266-75). Serious treatment-emergent adverse effects occurred in 9% of the 152 patients treated with filgotinib and 3 of the 67 patients treated with placebo. According to Dr. Sandborn, filgotinib is currently in phase 3 development trials for both Crohn's disease and UC. At the same time, results from an unpublished study presented at the annual Digestive Disease Week in 2017 found that 16 weeks of treatment with the investigational agent upadacitinib led to modified clinical remission in 37% of patients on the 24-mg bid dose, compared with 30% of patients in the 6-mg bid dose. There was also a dose response for endoscopic response. "Based on these data, this drug is now in a phase 3 trial, so lots of JAK inhibitors are coming along," he said.

Sphingosine-1–phosphate receptor 1 (S1P1) modulators currently under investigation include fingolimod (not studied in IBD), ozanimod, and etrasimod. "These modulators cause the S1P1 receptors that are expressed on the surface of positive lymphocytes to be eluded back into the cell, which leads to a reversible reduction in circulating lymphocytes in the blood," Dr. Sandborn explained. In a phase 2 trial, he and his associates found that UC patients who received ozanimod at a daily dose of 1 mg had a slightly higher rate of clinical remission, compared with those who received placebo, but the study was not sufficiently powered to establish clinical efficacy or assess safety (N Engl J. Med 2016;374:1754-62).

Dr. Sandborn reported having consulting relationships with Takeda, Genentech, Pfizer, Shire, Amgen, and many other pharmaceutical companies.

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Delayed ileal pouch AA had less postop events

BY DOUG BRUNK
Frontline Medical News

LAS VEGAS – Delayed creation of an ileal pouch anal anastomosis in patients with ulcerative colitis (UC) was associated with a lower risk of postoperative events, compared with creating the pouch at the time of initial surgery, results from an analysis of national data demonstrated.

"More than 600,000 Americans have UC, and 20%-30% of them require surgical management," Bharati Kochar, MD, said at the annual congress of the Crohn's & Colitis Foundation, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association. "The surgical procedure of choice for many UC patients is total proctocolectomy with ileal pouch anal anastomosis creation."

According to Dr. Kochar, an advanced fellow in inflammatory bowel diseases at the University of North Carolina at Chapel Hill, existing American medical literature regarding ileal pouch anal anastomosis (IPAA) comes mostly from quaternary care centers and compares one-stage procedures with multistage procedures.

"The risks between two- to three-stage procedures are not described, and there are no prospective national reports of postoperative adverse events after IPAA creation," she said.

Using data from the National Surgical Quality Improvement Program, Dr. Kochar and her associates conducted an observational cohort analysis of 2,390 adult patients with a postoperative diagnosis of UC who underwent IPAA procedures between 2011 and 2015. Their aims were to evaluate adverse events within 30 days after an IPAA creation and to compare adverse events between pouch creation at the time of colectomy and delayed pouch creation.

They also performed a subanalysis of total abdominal colectomy with ileostomy (TAC), the first stage in the delayed pouch procedures, versus pouch creation at the time of colectomy. Multivariable modified Poisson regression models were used to estimate risk ratios adjusted for age, sex, race, body mass index, smoking status, diabetes, preoperative albumin, and American Society of Anesthesiologists class.

Of the 2,390 patients, 1,571 had pouches created at the time of colectomy (group A), and 819 had delayed pouch creation (group B).

Compared with patients in group B, those in group A were older (a median age of 40 years vs. 37 years, respectively; *P* less than .01), were more likely to be on an immunosuppressant (51% vs. 15%; *P* less than .01), have a lower median preoperative albumin level (3.9 vs. 4.2; *P* less than .01), and a longer median length of stay (6 days vs. 5 days; *P* less than .01).

On unadjusted analyses, the researchers also observed that, at 30 days, patients in group A had significantly more major complications, such as mortality and cardiac arrest (12.4% vs. 8.7%; *P* less than .01); minor complications, such as superficial surgical site infections and pneumonia (11.8% vs. 6.1%; *P* less than .01); unplanned readmissions (statistically similar at 23.3% vs. 21.3%); and unplanned reoperations (7.7% vs. 3.8%; *P* less than .01).

After controlling for confounders, patients in group B were significantly less likely to have major complications (relative risk, 0.72), minor complications (RR, 0.48), unplanned readmissions (RR, 0.95), and unplanned reoperations (RR, 0.42).

In the subgroup analysis, Dr. Kochar and her associates observed that patients who underwent TAC were significantly older, compared with patients in group A (a median of 46 years vs. 40 years, respectively; *P* less than .01), and a higher proportion were on immunosuppressants (69% vs. 51%; *P* less than .01). "Despite these factors, the risk of adverse events after TAC was lower," Dr. Kochar said.

She acknowledged certain limitations of the study, including the inability to accurately determine the risk of linked surgeries together and the inability to assess institution and operator factors. Also, data were not collected for the purposes of studying inflammatory bowel disease.

"This is the first prospective assessment of morbidity following IPAA creation in UC patients from a national database," Dr. Kochar concluded. "Delayed pouch procedures are associated with a lower risk of unplanned reoperations and major and minor complications. Immunosuppression at the time of pouch creation may result in an increased risk of adverse events postoperatively. The findings can be valuable for preoperative risk assessment and postoperative management."

Dr. Kochar reported having no financial disclosures.

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SOURCE: Kochar B et al. Crohn's & Colitis Congress 2018 Clinical Abstract 11.

Higher BMI linked to problems in IBD patients

BY DOUG BRUNK
Frontline Medical News

LAS VEGAS – Higher body mass index among inflammatory bowel disease (IBD) patients is independently associated with an increased risk of treatment failure and IBD-related surgery or hospitalization, a single-center, retrospective cohort study demonstrated.

"The problem of IBD and obesity is on the rise," Soumya Kurnool said at the annual congress of the Crohn's & Colitis Foundation, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association. "Today, 15%-40% of IBD patients are obese. This is significant because there is a decreased prevalence of remission and an increased risk of relapse in obese IBD patients. These patients also have a higher annual burden of

Continued on following page

FDA issues safety alert for loperamide

BY LORI LAUBACH
Frontline Medical News

The Food and Drug Administration announced Jan. 30 that it has issued a MedWatch safety alert on the use of the over-the-counter (OTC) antidiarrhea drug, loperamide.

Currently, the FDA is working with manufacturers to use blister packs or other single-dose packaging and to limit the number of doses in a package.

The alert comes after receiving continuous reports of serious heart problems and deaths with the use of much higher than recommended doses of loperamide, mainly among people who are intentionally misusing or abusing the product, regardless of the addition of a warning to the medicine label and a previous communication. The FDA states that loperamide is a safe drug when used as directed.

Two particular methods of abuse are of concern. In some cases, abusers use other drugs together with loperamide in an effort to increase absorption and penetration across the blood-brain barrier, enhancing the euphoric effects of loperamide. Additionally, some individuals are using high doses of loperamide to mitigate against the symptoms of opioid withdrawal, according to the FDA.

Loperamide is approved to help control symptoms of diarrhea. The maximum recommended daily dose for adults is 8 mg per day for OTC use and 16 mg per day for prescription use. It acts on opioid receptors in the gut to slow the movement in the intestines and decrease the number of bowel movements.

It is noted that much higher than recommended doses of loperamide, either intentionally or unintentionally, can result in serious cardiac adverse events, including QT interval prolongation, torsade de pointes or other ventricular arrhythmias, syncope, and cardiac arrest. Health care professionals and patients can report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program.

In 2016, the FDA issued a Drug Safety Communication and added warnings about serious heart problems to the drug label of prescription loperamide and to the Drug Facts label of OTC loperamide products. The FDA is working to evaluate this safety issue and will update the public when more information is available.

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Continued from previous page

hospitalization."

Obesity also is associated with increased drug clearance for all biologic agents and higher odds of failing anti-TNF therapy in other immune-mediated inflammatory diseases, said Ms. Kurnool, a second-year student at the University of California, San Diego. "However, the research on the impact of obesity on treatment response to biologic agents in IBD is sparse and conflicting."

She and her associates set out to evaluate the effect of obesity on response to biologic therapy in patients with ulcerative colitis (UC). They conducted a single-center, retrospective cohort study of biologic-treated adults with UC who started therapy during 2011-2016. The researchers excluded patients who had undergone a prior colectomy, as well as those who were underweight at the time of starting a biologic agent and those who had fewer than 6 months of follow-up data.

The primary outcome was time to treatment failure, defined as a composite of IBD-related surgery, hospitalization, and/or treatment modification. Secondary outcomes were time to IBD-related surgery and/or hospitalization and whether the patient achieved endoscopic remission within 1 year of starting biologic therapy. They conducted multivariate Cox proportional hazard analyses after adjusting for key confounders.

Ms. Kurnool reported results from 160 patients with a median age of 36 years. Half were male, and the mean follow-up was 24 months. The median BMI of the cohort was 24.3 kg/m^2; 26% were overweight and 18% were obese. More than half of patients (55%) were on infliximab with weight-based dosing and 45% were on other fixed-dosing regimens, including 19% on vedolizumab. In terms of outcomes, 68% of patients experienced treatment failure. All who failed treatment underwent treatment modifications; 15% had IBD-related surgery, and 19% had IBD-related hospitalization.

After adjusting for age, sex, disease duration, prior hospitalization, prior anti-TNF therapy, steroid use, and albumin level, Ms. Kurnool and her associates found that every 1-kg/m^2 increase in BMI was associated with a 4% higher risk of treatment failure (adjusted hazard ratio, 1.04), an 8% higher risk of surgery or hospitalization (adjusted HR, 1.08), and a 6% lower risk of achieving endoscopic remission (adjusted HR, 0.94).

DOUG BRUNK/FRONTLINE MEDICAL NEWS

Soumya Kurnool is a second-year student at the University of California, San Diego School of Medicine.

"This increase in the risk of treatment failure and IBD-related surgery or hospitalization was consistent across strata of patients treated with infliximab and fixed-dosing regimens," she said. "Based on these findings, physicians should consider proactive monitoring in obese patients treated with biologic agents."

Ms. Kurnool reported having received a National Institutes of Health Short Term Training Grant from the University of California, San Diego.

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SOURCE: Kurnool S et al. Crohn's & Colitis Congress, Clinical Abstract 24.

Who is going down NASH path?

Fibrosis *from page 1*

minuria. If you do nothing and they don't die of cardiovascular disease, they're going to have a good chance of getting fibrosis."

As part of the large population-based Rotterdam study of individuals aged 45 years and older, researchers found that liver stiffness of 8 kPa or more by transient elastography was present in 5.6% of the study participants and was strongly associated with steatosis and diabetes (Hepatology. 2016;63:138-47). According to Dr. Cusi, individuals who have steatosis without diabetes face a 5%-10% risk of fibrosis, while those with steatosis and diabetes face a 15%-20% risk. "It's well established in a number of studies that if you have fibrosis, you're at high risk not only of cirrhosis, but also of hepatocellular carcinoma," he said. "The key thing is not detecting fat, which is not really the target. The target is if there's fibrosis or not." Three ways to assess for fibrosis include MR elastography, transient elastography (which is the most commonly used), and fibrosis marker panels.

Liver fibrosis likely starts with adipose tissue dysfunction, said Dr. Cusi, who authored a review on the pathophysiology of interactions between adipose tissue and target organs in obesity and the resulting clinical implications for the management of nonalcoholic steatohepatitis (Gastroenterology. 2012;142[4]:711-25.e6). "When you have insulin-resistant, sick adipose tissue, that leads to the accumulation of fat in the liver," he said. "Steatosis happens in about 70% of patients who are obese and have type 2 diabetes. The dilemma is how to know who is going down the path to fibrosis. Even if you get people who are matched for BMIs [body mass indexes] between 30 and 35 kg/m^2, there is a spectrum in which some individuals have very insulin-resistant adipose tissue and others less so. I would say that 1 out of 10 are metabolically healthy, and we don't understand exactly why."

In a recent cross-sectional analysis of 352 healthy individuals, Dr. Cusi and his associates found that intrahepatic triglyceride (IHTG) accumulation is strongly associated with adipose tissue insulin resistance, supporting the current theory of lipotoxicity as a driver of IHTG accumulation (Hepatology. 2017;65[4]:1132-44). The researchers observed that once IHTG accumulation reaches about 6%, skeletal muscle insulin resistance, hypertriglyceridemia, and low HDL cholesterol become fully established. "The next question is, How does this correlate with NASH?" Dr. Cusi said. "Our take is that there is a threshold effect. Once you have a critical amount of triglycerides in your liver, some individuals are going to activate pathways that are harmful. NASH is not something exclusive to individuals who are obese. Lean people can also develop NASH. The key feature is insulin resistance, not metabolic syndrome. Once you develop a fatty liver, your chances of NASH are comparable to that of an obese individual. The paradox is that lean individuals get a fatty liver, but when they get a fatty liver, they are at risk for NASH and for fibrosis."

The researchers observed that once IHTG accumulation reaches about 6%, skeletal muscle insulin resistance, hypertriglyceridemia, and low HDL cholesterol become fully established.

Why lean individuals develop NASH is not fully understood, but Dr. Cusi said he suspects that the problem develops at the mitochondrial level. Results from an unpublished animal model in which mice were fed a high–trans-fat diet for 24 weeks showed that the mice developed steatosis by week 8 and NASH by week 24. The mice had an increase in the tricarboxylic acid (TCA) cycle, which is typical of the NASH period, as well as an increase in ceramides. "Perhaps a unifying hypothesis would be that the development of NASH is linked to inflammation and to insulin signaling," Dr. Cusi said. "Not surprisingly, it had a number of effects on the mitochondria, and in this animal model it decreases the TCA." He noted that the biology of fibrosis remains unknown in humans. "What we have been familiar with is the high-triglyceride, low-HDL pattern," he said. "If you look at how that correlates with the amount of liver fat, it is basically a threshold effect. Once you have steatosis, you don't see much worse dyslipidemia, which is typical of these patients."

Recently published guidance from the American Association for the Study of Liver Diseases on the diagnosis and management of nonalcoholic fatty liver disease (NAFLD) suggests that patients require a weight loss of 3%-5% to improve steatosis, but a loss of 7%-10% to improve most histologic features of NASH, including fibrosis (Hepatology. 2018;67[1]:328-57). Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown. Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH. The procedure's impact on fibrosis is unknown.

The AASLD practice guideline notes that metformin is not recommended for treating NASH in adult patients, but pioglitazone improves liver histology in patients with and without type 2 diabetes with biopsy-proven NASH. "Pioglitazone has had the greatest benefit in terms of treatment effect, compared to placebo," Dr. Cusi said. "It's a generic drug; at the VA [Veterans Affairs], it costs 8 cents per tablet. I think that pioglitazone will be to NASH what metformin has been to type 2 diabetes. The most common side effect is weight gain, typically between 4 and 9 lbs. Risks and benefits should be discussed with each patient. It should not be used for NAFLD without biopsy-proven NASH." The guideline goes on to say that it's currently premature to consider GLP-1 (glucagonlike peptide–1) agonists for treating liver disease in patients with NAFLD or NASH. Meanwhile, vitamin E at 800 IU has been shown to improve liver histology in nondiabetic adults with NASH, but the risks and benefits should be discussed with each patient. Vitamin E is not recommended for NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

The AASLD practice guideline also states that the best evidence for using SGLT2 (sodium-glucose cotransporter–2) inhibitors in NAFLD comes from animal studies, which report a reduction in steatosis with and without weight loss. Clinical studies reporting a reduction in steatosis are limited. There are positive observational studies with a reduction in alanine aminotransferase and some studies that have shown a reduction in liver fat. "For me, the best option is to tailor treatment to the pathophysiology of the disease," Dr. Cusi said. "You reduce fat by weight loss in some way, or you change the biology of fat with a thiazolidinedione."

Dr. Cusi reported that he has received grant support from the Burroughs Wellcome Fund, the American Diabetes Association, and the National Institutes of Health.

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FDA adds boxed warning to obeticholic acid label

BY ELI ZIMMERMAN
Frontline Medical News

The Food and Drug Administration is requiring a boxed warning on the label for obeticholic acid (Ocaliva) to highlight the correct weekly dosing regimen after incorrect daily dosing caused severe liver injury in patients with moderate to severe primary biliary cholangitis (PBC).

"FDA is adding a new Boxed Warning, FDA's most prominent warning, to highlight this information in the prescribing information of the drug label," FDA officials said in a statement. "FDA is clarifying the current recommendations for screening, dosing, monitoring, and managing PBC patients with moderate to severe liver disease taking Ocaliva."

The warning is an update to a September 2017 MedWatch notice on the increased risk for patients from excessive dosing of obeticholic acid.

"Dosing higher than recommended in the drug label can increase the risk for liver decompensation, liver failure, and sometimes death. Routinely monitor all patients for biochemical response, tolerability, and PBC progression, and reevaluate Child-Pugh classification to determine if dosage adjustment is needed."

To report adverse medication events and side effects to the FDA, access the MedWatch program.

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Obesity affects the ability to diagnose liver fibrosis

BY IAN LACY
Frontline Medical News

Body mass index accounts for a 43.7% discordance in fibrosis findings between magnetic resonance elastography (MRE) and transient elastography (TE), according to a study from the University of California, San Diego.

"This study showed that the grade of obesity is also a significant predictor of discordancy between MRE and TE because the discordance rate between MRE and TE increases with the increase in BMI, wrote Cyrielle Caussy, MD, and her colleagues (Clin Gastrolenterol Hepatol. 2018 Jan 15. doi: 10.1016/j.cgh.2017.10.037)."

Dr. Caussy of the University of California, San Diego, and her colleagues had noted that MRE and TE had discordant findings in obese patients. To ascertain under what conditions TE and MRE produce the same readings, Dr. Caussy and her associates conducted a cross-sectional study of two cohorts with nonalcoholic fatty liver disease (NAFLD) who underwent contemporaneous MRE, TE, and liver biopsy. The training cohort involved 119 adult patients undergoing NAFLD testing from October 2011 through January 2017. The validation cohort, consisting of 75 adults with NAFLD undergoing liver imaging from March 2010 through May 2013, was formed to validate the findings of the training cohort.

The study revealed that BMI was a significant predictor of the difference between MRE and TE results and made it difficult to assess the stage of liver fibrosis (2-4 vs. 0-1). After adjustment for age and sex, BMI accounted for a 5-unit increase of 1.694 (95% confidence interval, 1.145-2.507; P = .008). As BMI increased, so did the discordance between MRE and TE (P = .0309). The discordance rate was significantly higher in participants with BMIs greater than 35 kg/m^2, compared with participants with BMIs below 35 (63.0% vs. 38.0%; P = .022), the investigators reported.

The study had both strengths and limitations. A strength of the study was the use of two cohorts, specifically the validation cohort. The use of the liver biopsy as a reference, which is the standard for assessing fibrosis, was also a strength of the study. A limitation was that the study was conducted at specialized, tertiary care centers using advanced imaging techniques that may not be available at other clinics. Additionally, the cohorts included a small number of patients with advanced fibrosis.

"The integration of the BMI in the screening strategy for the noninvasive detection of liver fibrosis in NAFLD should be considered, and this parameter would help to determine when MRE is not needed in future guidelines," wrote Dr. Caussy and her associates. "Further cost-effectiveness studies are necessary to evaluate the clinical utility of MRE, TE, and/or liver biopsy to develop optimal screening strategies for diagnosing NAFLD-associated fibrosis."

Dr. Chen, Dr. Yin, and Dr. Ehman have intellectual property rights and financial interests in elastography technology. Dr. Ehman also serves as a noncompensated CEO of Resoundant. Dr. Sirlin has served as a consultant to Bayer and GE Healthcare. All other authors disclosed no conflicts.

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SOURCE: Caussy C et al. Clin Gastrolenterol Hepatol. 2018 Jan 15. doi: 10.1016/j.cgh.2017.10.037.

AGA Resource
The AGA Obesity Practice Guide provides a comprehensive, multidisciplinary process to personalize innovative obesity care for safe and effective weight management. Learn more at www.gastro.org/obesity.

DDSEPeight
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Correct answer: C

Rationale
The initial management of dyspepsia depends on symptoms and presence of any "alarm features." In patients without "alarm features" presenting with symptoms suggestive of hepatobiliary or pancreatic causes, the initial diagnostic tests should include liver/pancreatic blood tests and abdominal imaging. For other dyspeptic patients without alarm features, initial management would include *H. pylori* testing (breath, stool antigen, or antibody) and/or empiric antisecretory (PPI) therapy. However, for patients who present with "alarm features" such as dysphagia, anemia, GI bleeding, anorexia, significant weight loss, etc., an upper endoscopy should be performed to evaluate for the presence of any upper GI tract malignancy. In this patient, the presence of microcytic anemia is an alarm feature. Tricyclic antidepressants such as amitriptyline may be used as treatment for functional dyspepsia, after organic causes have been ruled out.

Reference
1. Talley N.J., Vakil N.B., Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. Gastroenterology 2005;129:1756-80.

Q2. Correct answer: B

Rationale
The patient has a favorable anatomy for a surgical drainage procedure such as a lateral pancreaticojejunostomy (Peustow procedure). Surgery has been noted to provide superior pain relief over 5 years compared with endoscopy. Hospital costs and length of stay were similar between the groups. Continued medical therapy is unlikely to add further benefit on top of what she has already achieved. EUS-guided celiac plexus block will only provide temporary pain relief. There are limited long-term data on the effectiveness of total pancreatectomy with islet autotransplantation in alleviating pain.

References
1. Cahen D.L., Gouma D.J., Laramée P., et al. Gastroenterology. 2011;141(5):1690-5.
2. Conwell D.L., Lee L.S., Yadav D., et al. American pancreatic association practice guidelines in chronic pancreatitis. Pancreas. 2014;43:1143-62.

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Baby boomers are the hepatitis C generation

BY RICHARD FRANKI
Frontline Medical News

Increases in hepatitis C–related inpatient stays for baby boomers from 2005 to 2014 far outpaced those of older adults, while younger adults saw their admissions drop over that period, according to the Agency for Healthcare Research and Quality.

For adults aged 52-72 years, the rate of inpatient stays involving hepatitis C with or without hepatitis B, HIV, or alcoholic liver disease rose from 300.7 per 100,000 population in 2005 to 503.1 per 100,000 in 2014 – an increase of over 67%. For patients aged 73 years and older, that rate went from 104.4 in 2005 to 117.1 in 2014, which translates to a 12% increase, and for patients aged 18-51 years, it dropped 15%, from 182.5 to 155.4, the AHRQ said in a statistical brief.

Along with the increased hospitalizations, "acute hepatitis C cases nearly tripled from 2010 through 2015," the report noted, which was "likely the result of increasing injection drug use due to the growing opioid epidemic."

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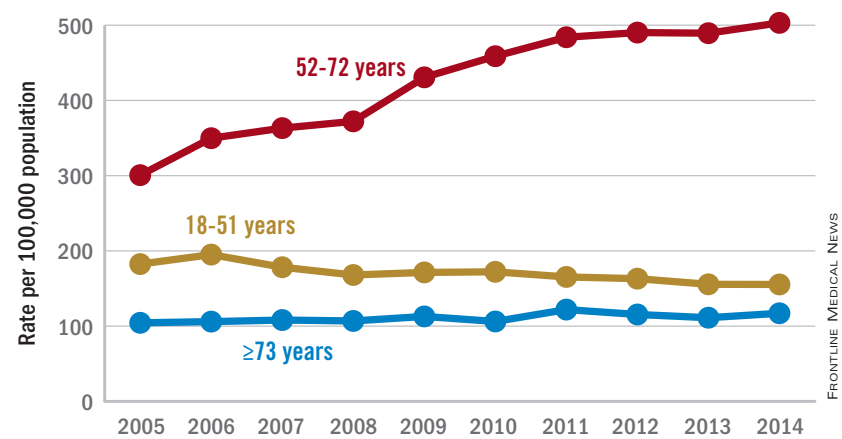
Inpatient stays involving hepatitis C by age group



Note: Based on data from the National Inpatient Sample.
Source: Agency for Healthcare Research and Quality

CLINICAL CHALLENGES AND IMAGES

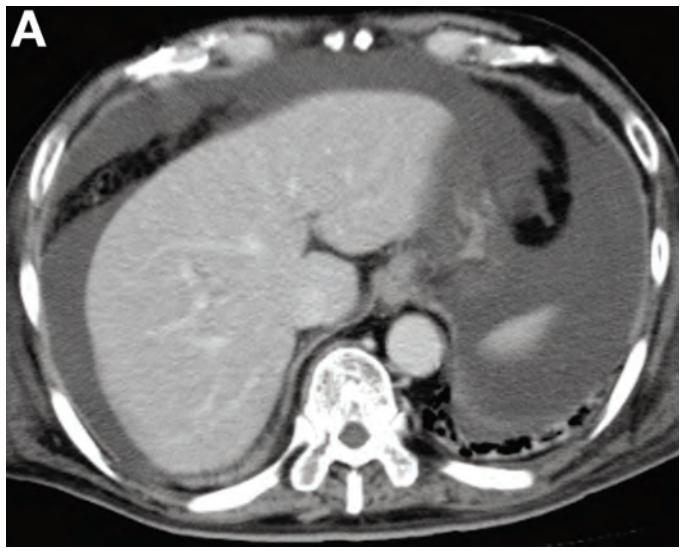
What is your diagnosis?

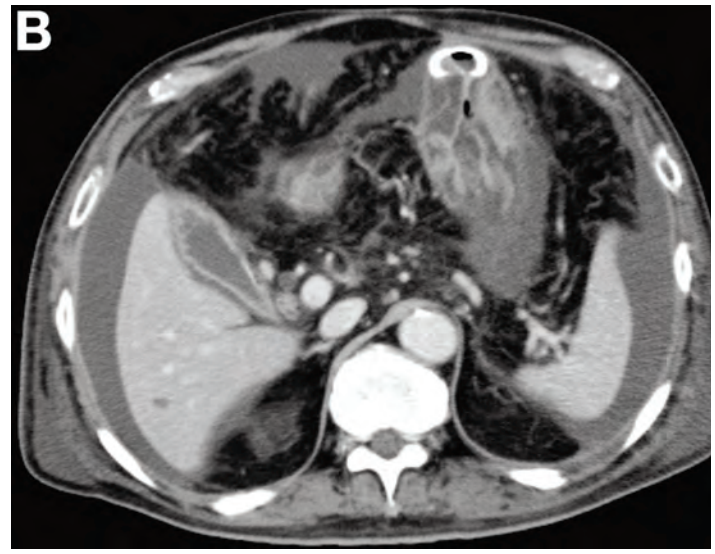
By Uichiro Fuchizaki, MD, Kazutoshi Yamada, MD, and Shogo Matsuda, MD. Published previously in Gastroenterology (2016;151[1]:40-2).

A 78-year-old man was admitted because of an exacerbation of interstitial pneumonia and was started on steroid therapy. On the next hospital day, he had a stroke. Because of persistent dysphagia, a percutaneous endoscopic gastrostomy tube was placed uneventfully 30 days later. On hospital day 64, he suddenly developed fever, jaundice, and abdominal distention, followed by hypotension, oliguria, and respiratory failure.

Laboratory tests revealed the following: white blood cell count, 44,300/mcL; serum albumin, 2.6 g/dL; aspartate aminotransferase, 1880 U/L; alanine aminotransferase, 1096 U/L; bilirubin, 1.21 mg/dL; and C-reactive protein, 13.5 mg/dL. He was diagnosed with septic shock and acute renal failure and was started on continuous hemodiafiltration and mechanical ventilation. Computed tomography (CT) of the abdomen showed marked ascites (Figure A, B), and a diagnostic paracentesis revealed a dark, greenish-brown fluid (Figure C) with a bilirubin level of 14.8 mg/dL.

The diagnosis is on page 40.





AGA Institute

A tool in early diagnosis

Blood test *from page 1*

Therapeutics at Johns Hopkins University, Baltimore, and his colleagues. The report was published in Science.

CancerSEEK tests for mutations in 2,001 genomic positions and eight proteins. The researchers examined a 61-amplicon panel with each amplicon analyzing an average of 33 base pairs within a gene. They theorized the test could detect between 41% and 95% of the cancers in the Catalog of Somatic Mutations in Cancer dataset. They next used multiplex-PCR techniques to minimize errors associated with large sequencing and identified protein biomarkers for early stage cancers that may not release detectable ctDNA.

See related story on page 38

The researchers used the technology to examine blood samples from 1,005 patients with stage I (20%), stage II (49%), or stage III (31%) cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, or breast prior to undergoing neoadjuvant chemotherapy. Participants had a median age of 64 years (range of 22-93 years). The healthy controls did not have a history of cancer, chronic kidney disease, autoimmune disease, or high-grade dysplasia.

The sensitivity of the test ranged from 98% in ovarian cancer to 33% in breast cancer, but the specificity was greater than 99%, with only 7 of 812 control participants having a positive result. "We could not be certain that the few 'false positive' individuals identified among the healthy cohort did not actually have an as-yet undetected cancer, but classifying them as false positives provided the most conservative approach to classification and interpretation of the data," the authors wrote.

Based on cancer stage, sensitivity for stage I cancers was 43%, for stage II 73%, and for stage III 78%. Again, sensitivity varied depending on cancer type, with 100% sensitivity for stage I liver cancer and 20% sensitivity for stage I esophageal cancer.

When tumor tissue samples from 153 patients with statistically significant ctDNA levels were analyzed, identical mutations were found in the plasma and tumor in 90% (138) of all cases.

The protein markers in the CancerSEEK test might also be able to anatomically locate malignancies. Using machine learning to analyze patients testing positive with CancerSEEK, the results narrowed the source of the cancer to two possible anatomical sites in approximately 83% of patients and to one anatomical site in approximately 63% of patients. Accuracy was highest for colorectal cancer and lowest for lung cancer.

As the study included otherwise healthy patients with known malignancies, the results need to be confirmed with prospective studies of incidence cancer types in a large population. Patients in the screening setting may have less advanced disease and other comorbidities that could impact the sensitivity and specificity of the CancerSEEK test, the researchers wrote.

The study was funded by multiple sources including grants from the National Institutes of Health. The authors reported various disclosures involving diagnostics and pharmaceutical companies.

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SOURCE: Cohen JD et al. Science 2018 Jan 18. doi: 10.1126/science.aar3247.

PERSPECTIVE

What are the clinically relevant questions answered by this test?

Molecular panels are here to stay – and the GI community will in some shape or form be impacted, be it in performing diagnostic procedures on test-positive patients, or risk-stratifying patients prior to testing.

DR. JUNG

The conceptual challenge is that it is not about what any given test measures – various panels use separate combination of markers from epigenetics to DNA mutations as well as whole or truncated proteins – but how well a specific test with its somewhat arbitrarily chosen components and cutoffs performs. And, more importantly, what the clinical implications of positive or negative test results are. And no one knows that. At least for now.

A recent report in Science from a group from the Ludwig Center for Cancer Genetics at Johns Hopkins proposes a new cancer blood test based on a very systematic and thoughtful approach to include select mutations in cell-free DNA and circulating proteins associated with various solid organ tumors. For validation, they used healthy and advanced but nonmetastatic cancer cohorts. Through stringent controls and a series of validations, the authors present a range of sensitivities for the various cancer types with an impressive specificity. This is a technically very strong approach with many nifty and thoughtful additions to give this test a very promising first foray – did anybody watch CNN?

While not ready for prime time, which is a tall order for a first report, the authors dutifully point out the need for a prospective real-life cohort validation. In the meantime, regardless of the outcome of this particular test, it is a repeated reminder that we need to stay abreast of the advances and the details of each molecular test, especially with a likely very diverse and distinct group of tests to choose from.

Many of us will be part of interpreting results and determining further management. Just as with hereditary cancer genetic panel testing, our technical ability may have stretched beyond our ability to fully understand the implications. Many questions will arise: What about true false positives? False negatives? Intervals? Can such tests replace other screening? How to choose any given test over the other? Should tests be combined or alternated? The tests will be technically refined and are here to stay – we need to get to work on finding answers to the clinically relevant questions.

Barbara Jung, MD, AGAF, is the Thomas J. Layden Endowed Professor and chief of the division of gastroenterology and hepatology, University of Chicago.

FDA approves lutetium Lu 177 dotatate for GEP-NETs

BY LORI LAUBACH
Frontline Medical News

The Food and Drug Administration has approved the first radiopharmaceutical, lutetium Lu 177 dotatate (Lutathera), for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Approval is based on two studies, including the phase 3, NETTER-1, that compared lutetium Lu 177 dotatate plus octreotide to octreotide alone, and a subset of patients from an expanded access program in the Netherlands in patients with somatostatin receptor positive tumors, the FDA said in a statement.

The NETTER-1 study included patients who had inoperable midgut NETs progressing under standard-dose octreotide treatment and overexpressing somatostatin receptors. The primary endpoint was met, showing a 79% reduction in risk of disease progression or death in the study arm compared with the control (hazard ratio, 0.21; 95% CI, 0.13-0.32; *P* less than .0001). There was a 48% reduction in the estimated risk of death with lutetium Lu 177 dotatate treatment compared to treatment with octreotide alone at a preplanned interim overall survival analysis (HR, 0.52; 95% CI, 0.32-0.84).

In the expanded access study, complete or partial tumor shrinkage was reported in 16% of the patients in the subset of 360 patients with GEP-NETs.

Common side effects include lymphopenia, increased GGT, AST and/or ALT, vomiting, nausea, hyperglycemia and hypokalemia. Serious side effects include myelosuppression, secondary myelodysplastic syndrome and leukemia, renal toxicity, hepatotoxicity, neuroendocrine hormonal crises, and infertility. Patients taking lutetium Lu 177 dotatate are exposed to radiation; exposure of other patients, medical personnel, and household members should be limited according to the FDA.

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Cancer rates haven't budged despite colonoscopy quality efforts

BY HEIDI SPLETE
Frontline Medical News

The number of colorectal cancers diagnosed after a colonoscopy remained consistent at approximately 8% over a 15-year period despite the introduction of quality improvement measures, according to data from a population-based cohort study of more than 1 million individuals in Canada.

"It is believed that the majority of PCCRCs [postcolonoscopy colorectal cancers] arise due to cancers or near cancers that were either missed or incompletely treated during colonoscopy," wrote Sanjay K. Murthy, MD, of the University of Ottawa, and colleagues.

Established quality improvement measures included adenoma detection rate, cecal intubation rate, colonoscopy withdrawal time, and endoscopy training standards, but how well the measures have been implemented remains uncertain, the researchers said. In a study published in Gastrointestinal Endoscopy (2018 Jan 6. doi: 10.1016/j.gie.2017.12.027), the researchers assessed data from 1,093,658 eligible adults aged 50-74 years over a 15-year period. The time period was divided into three sections: July 1, 1996, to June 30, 2001; July 1, 2001, to June 30, 2006; and July 1, 2006, to Dec. 31, 2010.

The number of colonoscopies increased during the study period, from 305 per 10,000 people in 1996-1997 to 870 per 10,000 people in 2010-2011.

Comparing the 2006-2010 and 1996-2001 time periods yielded adjusted odds of PCCRC, distal PCCRC, and proximal PCCRC of 1.14, 1.11, and 1.14, respectively; the trends were not affected by endoscopist specialty or institutional setting.

"Our findings are concerning for lack of improvement in colonoscopy practice quality in Ontario, particularly in the wake of greater emphasis having been placed on colonoscopy quality metrics during the study period," the researchers said. The findings contrast with the decline in PCCRC rates in the United Kingdom reported in a previous study of a similar time period, they noted.

The study findings were limited by several factors, including possible patient and outcome misclassification, and an unvalidated definition for PCCRC. Although more research is needed in other jurisdictions to confirm, the results "call for increased population-based practice audit as well as endoscopy educational programs and certification requirements."

The study was supported by a research grant to Dr. Murthy from the University of Ottawa. The researchers had no conflicts to disclose.

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SOURCE: Murthy SK et al. Gastrointest Endosc. 2018 Jan 6. doi: 10.1016/j.gie.2017.12.027.

PERSPECTIVE

What is holding back 'quality'?

Postcolonoscopy colorectal cancers (PCCRCs) are those cancers that occur between 6 and 36 months after a complete colonoscopy. Most of these cancers grow from cancers or near cancers missed or incompletely resected during the baseline colonoscopy. Clinical researchers have published extensively about reasons for missed lesions and we know that age, female sex, and proximal location of cancers increase rates of PCCRC. GI societies worldwide have developed training initiatives, performance metrics (adenoma detection rate or ADR, withdrawal time, and prep quality documentation), and postcolonoscopy guidelines, all intended to mitigate risk of PCCRCs. It would be nice to know whether such efforts have made a difference.


DR. ALLEN

Murthy and colleagues studied PCCRC rates in Ottawa, Canada, during three different time periods to determine whether quality and educational efforts affected PCCRC rates. More than 99% of this population has health care covered under a single public payer system where all encounters are tracked. Using population-level data derived from over 1 million people they identified cancers diagnosed within 36 months of a colonoscopy and compared three 5-year periods (1996-2001, 2001-2006, and 2006-2010).

Their method of calculating PCCRC rates essentially says, "If I am destined to develop CRC in the next 3 years, what is my chance of a false-negative colonoscopy?" The question posed above yields "rates" that would terrify patients (4%-10%) without a detailed explanation (it took me about an hour of focused attention to finally understand this methodology). In essence, if we could, a priori, identify and examine only patients who have a prevalent cancer or near cancer, how close can we come to 100% accuracy with a colonoscopy? Turns out, that rate is somewhere between 90% and 96% and really hasn't changed over time. Thus, these studies speak to the impact of our efforts around colonoscopy quality.

The discouraging conclusion from Murthy's analysis is that despite substantial efforts, false-negative colonoscopy rates have remained around 8% (in Ottawa) since 1996. Of note, this contrasts with studies out of England, where a national, focused quality improvement effort has been ongoing for over a decade and has made a dent (although slight) in PCCRC rates. This is a provocative study that deserves your attention.

John I. Allen MD, MBA, AGAF, professor of medicine, department of gastroenterology and hepatology, University of Michigan, Ann Arbor, and Editor in Chief of GI & Hepatology News.

Colorectal cancer deaths projected for 2018

BY RICHARD FRANKI
Frontline Medical News

Colon and rectal cancer mortality is expected to be about 15.5/100,000 population in 2018, with the highest rate in West Virginia and the lowest in Utah.

Approximately 50,630 deaths from colorectal cancer are predicted for the year in the United States by the American Cancer Society (ACS) in its Cancer Facts & Figures 2018, based on analysis of 2001-2015 data from the National Center for Health Statistics.

The expected number of deaths for 2018, coupled with a current population estimate of nearly 326 million, works out to an expected death rate of 15.5/100,000 population. The Census Bureau estimates for the state populations and the deaths projected by the ACS produce expected death rates of 23.6/100,000 for West Virginia and 9.0 for Utah.

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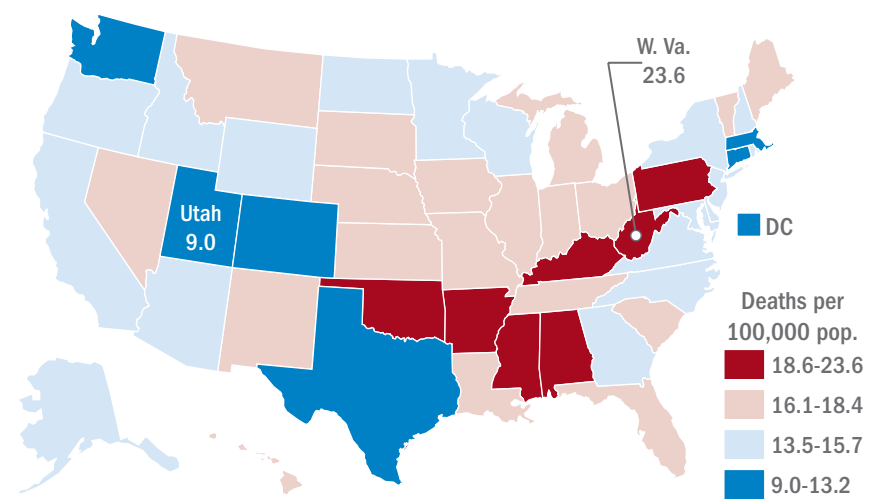
Estimated colon and rectal cancer death rates for 2018



Note: Based on 2001-2015 mortality data from the National Center for Health Statistics.
Source: American Cancer Society

Circulating tumor cell assay promising for CRC screen

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – A new blood-based assay that measures circulating tumor cells (CTCs) shows good performance in detecting colorectal cancer and precancer, investigators reported at the 2018 GI Cancers Symposium.

Although colorectal cancer screening is a grade A recommendation of the U.S. Preventive Services Task Force, poor uptake remains problematic and contributes to more advanced disease at diagnosis, noted lead investigator Wen-Sy Tsai, MD, assistant professor at Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan.

"Currently, one-third of Americans have never been screened for colorectal cancer," he said, due in part to reluctance to undergo colonoscopy and poor compliance with stool tests. Further complicating matters, the fecal immunochemical test (FIT) has a high false-positive rate.

He and his coinvestigators tested the new assay, called CMx (CTCs in Maximum), among 620 individuals in Taiwan who underwent colonoscopy – some with colorectal cancer, some with precancerous lesions, and some healthy. Results showed the assay's sensitivity was nearly 87% for cancer and 77% for precancerous lesions. Specificity exceeded 97%.

"The CMx assay is capable of detecting ... early-stage cancer with a low false-positive rate. As it is a blood test, higher compliance will lead to better outcomes," Dr. Tsai proposed. "Because the mechanism of CTC dissemination is similar, the CTC assay can be applied in other cancer types such as prostate, breast, and lung cancer."

Dr. Wen-Sy Tsai is assistant professor at Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Dr. Douglas A. Corley is clinical professor and gastroenterologist at the University of California, San Francisco.

PHOTOS SUSAN LONDON/FRONTLINE MEDICAL NEWS

The investigators are also identifying collaborators for testing the new assay among U.S. populations, he noted.

"Screening tests offer some of the greatest potential for getting to zero colorectal cancer deaths," said invited discussant Douglas A. Corley, MD, PhD, AGAF, clinical professor and gastroenterologist at the University of California, San Francisco, and a research scientist at Kaiser Permanente, San Francisco.

CTCs are especially attractive for screening because they could be both sensitive and specific, he said. "Unlike something such as fecal immunotesting, which is not testing specifically for cancer, or colonoscopy, which is quite invasive and detects a lot of things that may never progress to cancer, CTCs offer this potential," said Dr. Corley.

See related story on page 34

Challenges of interpreting new screening tests include their heavy dependence on the population being tested and the need for replication, according to Dr. Corley. For example, initial results for the septin 9 methylated DNA blood test looked very good, with sensitivity of about 90% (BMC Med. 2011;9:133), but after its testing in 14 populations, a meta-analysis showed that pooled sensitivity was just 67% (Biomed Rep. 2017;7[4]:353-60).

"Circulating tumor markers are an incredibly interesting target for screening, particularly because of their potential for being very specific for what you are looking for, and potentially markedly decreasing the subsequent follow-up that would need to be done for invasive tests such as colonoscopy," Dr. Corley said. "However, this [CTC assay] really requires confirmation in screening populations, especially given some of the information we have from prior tests."

Study details

Dr. Tsai's team studied 327 patients with colorectal cancer of all stages, 111 patients with precancerous lesions (adenomas, advanced adenomas, carcinoma in situ/stage 0), and 182 healthy controls. All had blood drawn for the CTC assay before undergoing colonoscopy. Results of each test were ascertained with blinding to the results of the other.

CTCs are rarely shed into the circulation from precancerous lesions, with approximate density of only 1 per billion blood cells, Dr. Tsai said. The CMx assay (manufactured by CellMax Life) is able to detect these cells with high sensitivity through use of advanced technologies such as affinity-based microfluidics and a biomimetic surface coating.

The assay is performed with just 2 mL of whole blood. CTCs are defined as intact nucleated cells staining positive for CD20 and negative for CD45; they were combined with patient age in an algorithm, ultimately producing a risk score.

Study results showed that the CTC assay had an accuracy of 87.9% in the entire cohort, reported Dr. Tsai. The false-positive rate was just 3.3%, and the false-negative rate was 15.8%.

Sensitivity was 84.0% overall (76.6% for precancer and 86.9% for cancer), specificity was 97.3% overall (97.3% and 97.3%), and area under the receiver operating characteristic curve was 0.87 overall (0.84 and 0.88).

Dr. Tsai noted that the CTC assay's sensitivity of nearly 77% for precancer compares favorably with that of a variety of other screening tests, such as the stool guaiac test for fecal occult blood (2%-10%), FIT alone (23.8%), and a stool DNA test combined with FIT (42%), and, in fact, falls within the range reported for colonoscopy (76%-94%).

The symposium was sponsored by the American Gastroenterological Association, the American Society for Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology.

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SOURCE: Tsai W et al., ASCO GI Abstract 556.

AGA Guideline: Use goal-directed fluid therapy, early oral feeding in acute pancreatitis

BY AMY KARON
Frontline Medical News

Patients with acute pancreatitis should receive "goal-directed" fluid therapy with normal saline or Ringer's lactate solution rather than hydroxyethyl starch (HES) fluids, states a new guideline from the AGA Institute.

In a single-center randomized trial, hydroxyethyl starch fluids conferred a 3.9-fold increase in the odds of multiorgan failure (95% confidence interval for odds ratio, 1.2-12.0) compared with normal saline in patients with acute pancreatitis, wrote guideline authors Seth D. Crockett, MD, MPH, of the University of North Carolina, Chapel Hill, and his associates. This trial and another randomized study found no mortality benefit for HES compared with fluid resuscitation. The evidence is "very low quality" but mirrors the critical care literature, according to the experts. So far, Ringer's lactate solution and normal saline have shown similar effects on the risk of organ failure, necrosis, and mortality, but ongoing trials should better clarify this choice, they noted (Gastroenterology. doi: 10.1053/j.gastro.2018.01.032).

The guideline addresses the initial 2-week period of treating acute pancreatitis. It defines goal-directed fluid therapy as titration based on meaningful targets, such as heart rate, mean arterial pressure, central venous pressure, urine output, blood urea nitrogen concentration, and hematocrit. Studies of goal-directed fluid therapy in acute pancreatitis have been unblinded, have used inconsistent outcome measures, and have found no definite benefits over nontargeted fluid therapy, note the guideline authors. Nevertheless, they conditionally recommend goal-directed fluid therapy, partly because a randomized, blinded trial of patients with severe sepsis or septic shock (which physiologically resembles acute pancreatitis) had in-hospital mortality rates of 31% when they received goal-directed fluid therapy and 47% when they received standard fluid therapy (P = .0009).

The guideline recommends against routine use of two interventions: prophylactic antibiotics and urgent endoscopic retrograde cholangiopancreatography (ERCP) for patients with acute pancreatitis. The authors note that no evidence supports routine prophylactic antibiotics for acute pancreatitis patients without cholangitis, and that urgent ERCP did not significantly affect the risk of mortality, multiorgan failure, single-organ failure, infected pancreatic and peripancreatic necrosis, or necrotizing pancreatitis in eight randomized controlled trials of patients with acute gallstone pancreatitis.

The guideline defines goal-directed fluid therapy as titration based on meaningful targets, such as heart rate, mean arterial pressure, central venous pressure, urine output, blood urea nitrogen concentration, and hematocrit.

The guideline strongly recommends early oral feeding and enteral rather than parenteral nutrition for all patients with acute pancreatitis. In 11 randomized controlled trials, early and delayed feeding led to similar rates of mortality, but delayed feeding produced a 2.5-fold higher risk of necrosis (95% CI for OR, 1.4-4.4) and tended to increase the risk of infected peripancreatic necrosis, multiorgan failure, and total necrotizing pancreatitis, the authors wrote. In another 12 trials, enteral nutrition significantly reduced the risk of infected peripancreatic necrosis, single-organ failure, and multiorgan failure compared with parenteral nutrition.

Clinicians continue to debate cholecystectomy timing in patients with biliary or gallstone pancreatitis. The guidelines strongly recommend same-admission cholecystectomy, citing a randomized controlled trial in which this approach markedly reduced the combined risk of mortality and gallstone-related complications (OR, 0.2; 95% CI, 0.1-0.6), readmission for recurrent pancreatitis (OR, 0.3; 95% CI, 0.1-0.9), and pancreaticobiliary complications (OR, 0.2; 95% CI, 0.1-0.6). "The AGA issued a strong recommendation due to the quality of available evidence and the high likelihood of benefit from early versus delayed cholecystectomy in this patient population," the experts stated.

Patients with biliary pancreatitis should be evaluated for cholecystectomy during the same admission, while those with alcohol-induced pancreatitis should receive a brief alcohol intervention, according to the guidelines, which also call for better studies of how alcohol and tobacco cessation measures affect risk of recurrent acute pancreatitis, chronic pancreatitis, and pancreatic cancer, as well as quality of life, health care utilization, and mortality.

The authors also noted knowledge gaps concerning the relative benefits of risk stratification tools, the use of prophylactic antibiotics in patients with severe acute pancreatitis or necrotizing pancreatitis, and the timing of ERCP in patients with severe biliary pancreatitis with persistent biliary obstruction.

The guideline was developed by the AGA Institute. The authors disclosed no conflicts of interest.

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SOURCE: Crockett SD et al. Gastroenterology. doi: 10.1053/j.gastro.2018.01.032.

Doctors to Congress: Keep Part B drug payments out of MIPS adjustment

BY GREGORY TWACHTMAN
Frontline Medical News

Physician specialists are calling on Congress to isolate Medicare Part B drug reimbursements from payment adjustments under the Merit-Based Incentive Payment System (MIPS).

A coalition of medical societies, large group practices, and patient advocacy groups has asked for an "intervention this year with a technical correction that ensures the [MIPS] score adjustment is not applied to Part B drug payments," according to a Jan. 18 letter sent to the leaders of the Senate Finance Committee, House Energy and Commerce Committee, and the House Ways and Means Committee. "Since the 2018 MIPS year has begun, it is imperative that Congress acts quickly to ensure that patient access to critical treatments is not negatively impacted."

Among the groups signing the letter are the American Academy of Dermatology, American Gastroenterological Association, American College of Rheumatology, American Academy of Neurology, and the American Society of Clinical Oncology.

Under MIPS, physicians are scored based on their performance across three categories: quality, improvement activities, and advancing care information. A fourth category, cost, is planned but not yet included in the score (although cost doesn't impact adjustments until 2020, it is part of the 2018 program year). Medicare payments, which currently include Part B drug reimbursements, are subject to bonuses and penalties based on performance scores.

In their November 2017 update to the Quality Payment Program, which includes MIPS, officials at the Centers for Medicare & MedicaidServices (CMS) said they would be moving forward with including Part B drug payments in the MIPS adjustment.

"This application of the adjustment ... is a significant departure from current policy and would disproportionately affect certain specialties," according to the coalition's letter.

Certain specialties, including rheumatology, oncology, and ophthalmology, have more to lose under the current policy because these specialists administer more Part B drugs than other specialists, according to health care consultancy Avalere Health.

For gastroenterologists, the primary concern with the application of the MIPS payment adjustment to Part B drugs is patient access to the biologics and biosimilars used to treat inflammatory bowel disease including Crohn's disease and ulcerative colitis. Under CMS's policy, gastroenterologists facing a penalty or negative payment adjustment may have Part B drug payments fall below what it costs to buy the Part B drug. Since Medicare payment for Part B drugs is based on average sales price, affected practices are more likely to be small, have a smaller number of patients on a Part B drug or prescribe a broader range of Part B drugs to patients. As MIPS payment adjustments increase each year, the impact of the policy is expected to touch more practices and bring larger deficits, further eroding access to the biologics and biosimilars used to treat IBD.

"Certain specialists administer more Part B drugs than others and, therefore, may be exposed to significant financial risk and payment swings year-over-year under the CMS proposal," John Feore, director at Avalere, said in a statement.

In 2018, physicians in those specialties could see drug payments increase or decrease by as much as 16%, according to Avalere research.

The policy likely will have an even greater effect on smaller practices and those in rural settings and could lead to access issues, according to the coalition letter.

"Some patients already face access challenges because the budget sequester has eroded reimbursements to physicians, and this policy would exacerbate these problems," the letter states. "Patients would be left with fewer locations where they could receive care, resulting in less access and higher costs. A growing number of patients would then have to seek care in a hospital, which would result in higher out-of-pocket expenses and, particularly in rural communities, may require traveling longer distances to receive care."

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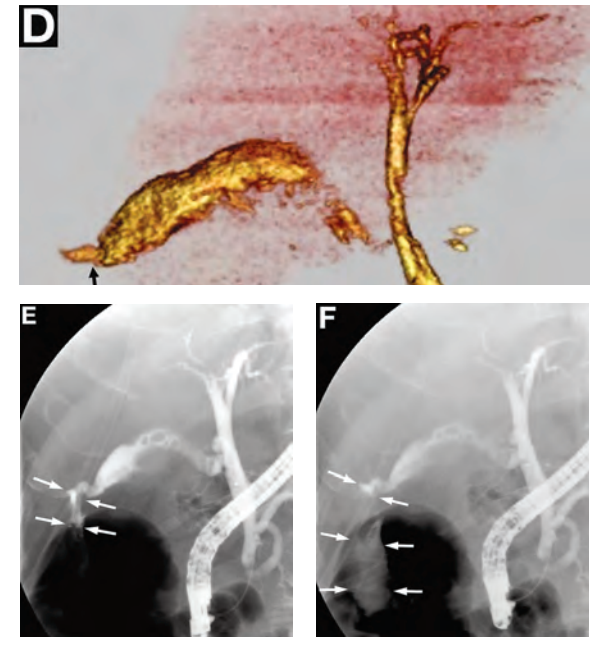
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 33: Spontaneous gallbladder perforation

No definite site of perforation was observed in the biliary tract by CT. However, with a suspicion of biliary tract perforation, 3-dimensional drip-infusion CT cholangiography was performed, which revealed a leakage of contrast medium from the gallbladder fundus (Figure D, arrow) into the subhepatic space, leading to a diagnosis of spontaneous gallbladder perforation. Endoscopic retrograde cholangiography confirmed the perforation at the same site (Figure E, F, arrows). An endoscopic nasobiliary drainage tube was placed, and bile was aspirated continuously. Four weeks later, when the general condition of the patient stabilized, cholecystectomy was performed. Histologic examination showed a 3-mm perforation in the gallbladder fundus with marked necrosis of the gallbladder wall associated with chronic cholecystitis. No stones were found. He had an uneventful recovery and was discharged in an improved condition.

Gallbladder perforation is a rare but life-threatening complication of cholecystitis with or without stones, with a recently reported mortality rate of 9.5%.[1] Niemeier[2] classified the condition into three types: type I (acute), free perforation and generalized peritonitis; type II (subacute), localized peritonitis and pericholecystic abscess; and type III (chronic), cholecystoenteric fistula. These classifications are still in use. Our patient had a type I perforation. The most common site of perforation is the fundus because of its poor blood supply. Predisposing factors for spontaneous gallbladder perforation include cholelithiasis, infections, diabetes mellitus, atherosclerosis, and steroid therapy, which was observed in the present case. The diagnosis is suggested by ultrasonography, CT, magnetic resonance imaging, endoscopic retrograde cholangiography, or cholescintigraphy. As observed in the present case, drip-infusion CT cholangiography provides high-quality images of the biliary system; however, the availability of intravenous cholangiographic contrast media is limited to a few countries.[3] The difficulties in diagnosis cause a delay in treatment and lead to high morbidity and mortality. Gallbladder perforation should be considered as a differential diagnosis in patients presenting with peritonitis with an unknown etiology.



AGA Institute

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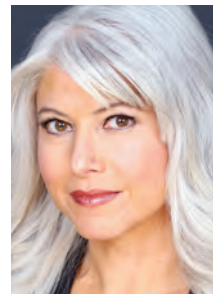
PRACTICE MANAGEMENT TOOLBOX:

Making social media work for your practice

BY DARRELL M. GRAY II, MD, MPH, AND DEBORAH A. FISHER, MD, MHS, AGAF

DR. GRAY



DR. FISHER

Social media use is ubiquitous and, in the digital age, it is the ascendant form of communication. Individuals and organizations, digital immigrants (those born before the widespread adoption of digital technology), and digital natives alike are leveraging social media platforms, such as blogs, Facebook, Twitter, YouTube, and LinkedIn, to curate, consume, and share information across the spectrum of demographics and target audiences. In the United States, 7 in 10 Americans are using social media and, although young adults were early adopters, use among older adults is increasing rapidly.[1]

Furthermore, social media has cultivated remarkable opportunities in the dissemination of health information and disrupted traditional methods of patient–provider communication. The days when medically trained health professionals were the gatekeepers of health information are long gone. Approximately 50% of Americans seek health information online before seeing a physician.[2] Patients and other consumers regularly access social media to search for information about diseases and treatments, engage with other patients, identify providers, and to express or rate their satisfaction with providers, clinics, and health systems.[3-5] In addition, they trust online health information from doctors more than that from hospitals, health insurers, and drug companies.[6] Not surprisingly, this has led to tremendous growth in use of social media by health care providers, hospitals, and health centers. More than 90% of U.S. hospitals have a Facebook page and 50% have a Twitter account.[7]

Although adoption of social media has been slow among GIs and hepatologists, it is growing. In a study published in 2015, Davis et al.[8] found that only 48% of GI providers reported never using social media. More recently, in March 2017, we conducted a survey of AGA members subscribed to the AGA eDigest. Of the 69 participants, one-third reported using at least one social media platform multiple times per day and 56% expressed interest in expanding their social media presence. Chiang et al.[9] even developed GI hashtag ontology (hashtag refers to a phrase that is preceded by # and is used to identify and collate topics of interest, i.e., #coloncancer) as a means to allow lay and health professional social media users to curate medical information more easily. These data are particularly interesting in light of studies suggesting that patients with inflammatory bowel disease and chronic viral hepatitis, chronic diseases that commonly are managed by GI and hepatology providers, use social media in the management of their disease. Patients with these conditions also value interaction with health care professionals on social media.[10,11]

There is ample opportunity to close the gap between patient and health care provider engagement in social media, equip providers with the tools they need to be competent consumers and sharers of information in this digital exchange, and increase the pool of evidence-based information on GI and liver diseases on social media.[12] However, there is limited published literature tailored to GIs and hepatologists. The goal of this article, therefore, is to provide a broad overview of best practices in the professional use of social media and highlight examples of novel applications in clinical practice.

Content from this column was originally published in the "Practice Management: The Road Ahead" section of *Clinical Gastroenterology and Hepatology* (2017;15[11]:1651-4).

Getting started and maintaining a presence on social media

Social media can magnify your professional image, amplify your voice, and extend your influence much faster than other methods. It also can be damaging if not used responsibly. Thus, we recommend the following approaches to responsible use of social media and to cultivating your social media presence based on current evidence, professional organizations' policy statements, and our combined experience. We initially presented these strategies during a Meet-the-Professor Luncheon at Digestive Disease Week® in Chicago (http://www.ddw.org/education/session-recordings).

First, establish personal objectives and/or goals for using social media. It is with these in mind that you select social media platforms on which to create a digital profile and footprint. They also can serve as guiding principles for the content that you share and individuals or groups with whom you engage. For example, if your goals include disseminating evidence-based content on liver diseases to a broad audience and connecting with a network of key opinion leaders and patient-oriented groups who share this interest and/or expertise, Twitter may be an ideal option for you given its vast user base and flexibility in both posting multimedia content such as pictures, videos, and links to publications, and tailoring the content you receive to specific individuals and groups.

Second, find a mentor to provide hands-on advice. This is particularly true if your general familiarity with the social media platforms is limited. If this is not available through your network of colleagues or workplace, we recommend exploring opportunities offered through your professional organization(s) such as the aforementioned Meet-the-Professor Luncheon at DDW.

Third, know the privacy setting options on your social media platform(s) of choice. For example, on Facebook and Twitter, you can select an option that requests your permission before a friend or follower is added to your network. You also can tailor who (such as friends or followers only) can access your posted content directly. However, know that your content still may be made public if it is shared by one of your friends or followers.

Fourth, nurture your social media presence by sharing credible content deliberately, regularly, and, when appropriate, with attribution.

Fifth, diversify your content within the realm of your predefined objectives and/or goals and avoid a singular focus of self-promotion or the appearance of self-promotion. Top social media users suggest, and the authors agree, that your content should be only 25%-33% of your posts.

Sixth, thoroughly vet all content that you share. Avoid automatically sharing articles or posts because of a catchy headline. Read them before you post them. There may be details buried in them that are not credible or with which you disagree.

Seventh, build community by connecting and engaging with other users on your social media platform(s) of choice.

Eighth, integrate multiple media (i.e., photos, videos, infographics) and/or social media platforms (i.e., embed link to YouTube or a website) to increase engagement.

Ninth, adhere to the code of ethics,

Continued on following page

Table 1. Examples of social media metrics to include in dossier for promotion and tenure

Demonstration of excellence
Evidence of recognition for expertise in clinical field.
Peer-reviewed and non–peer-reviewed publications.
Collaborations within and/or outside of your institution resulting from social media engagement.
Data supporting excellence in clinical care, teaching, and/or leadership from social media engagement.
Demonstration of reputation
Evidence of being a key opinion leader.
Invited lectures at local, regional, national, and/or international meetings, webinars, or podcasts.
Invitations to serve on national committees.
Media requests and quotes.
Demonstration of impact
Evidence of activities or innovations that positively influenced the clinical or research practice within field of expertise.
Feedback from followers on value of social media posts.
Development and implementation of policy, curricula, or practices within an institution and/or professional organization.
Awards or recognition related to social media engagement.

Continued from previous page

governance, and privacy of the profession and of your employer.

Best practices: Privacy and governance in patient-oriented communication on social media

Two factors that have been of pivotal concern with the adoption of social media in the health care arena and led to many health care professionals being laggards as opposed to early adopters are privacy and governance. Will it violate the patient–provider relationship? What about the Health Insurance Portability and Accountability Act? How do I maintain boundaries between myself and the public? These are just a few of the questions that commonly are asked by those who are unfamiliar with social media etiquette for health care professionals. We highly recommend reviewing the position paper regarding online medical professionalism issued by the American College of Physicians and the Federation of State Medical Boards as a starting point.[13] We believe the following to be contemporary guiding principles for GI health providers for maintaining a digital footprint on social media that reflects the ethical and professional standards of the field.

First, avoid sharing information that could be construed as a patient identifier without documented consent. This includes, but is not limited to, an identifiable specimen or photograph, and stories of care, rare conditions, and complications. Note that dates and location of care can lead to identification of a patient or care episode.

Second, recognize that personal and professional online profiles are discoverable. Many advocate for separating the two as a means of shielding the public from elements of a private persona (i.e., family pictures and controversial opinions). However, the capacity to share and find comments and images on social media is much more powerful than the privacy settings on the various social media platforms. If you establish distinct personal and professional profiles, exercise caution before accepting friend or follow requests from patients on your personal profile. In addition, be cautious with your posts on private social media accounts because they rarely truly are private.

Third, avoid providing specific medical recommendations to individuals. This creates a patient–provider relationship and legal duty. Instead, recommend consultation with a health care provider and consider providing a link to general information on the topic (e.g., AGA information for patients at www.gastro.org/patientinfo).

Fourth, declare conflicts of interest, if applicable, when sharing information involving your clinical, research, and/or business practice.

Fifth, routinely monitor your online presence for accuracy and appropriateness of content posted by you and by others in reference to you. Know that our profession's ethical standards for behavior extend to social media and we can be held accountable to colleagues and our employer if we violate them.

Many employers have become savvy to issues of governance in use of social media and institute policy recommendations to which employees are expected to adhere. If you are an employee, we recommend checking with your marketing and/or human resources department(s) about this.

Novel applications for social media in clinical practice

Social media has been shown to be an effective medium for medical education through virtual journal clubs, moderated discussions or chats, and video sharing for teaching procedures, to name a few applications. Social media is used to collect data via polls or surveys, and to disseminate and track the views and downloads of published works. It is also a source for unsolicited, real-time feedback on patient experience and engagement, and, more simply, for solicited feedback for patient satisfaction ratings.

Academic institutions increasingly are recognizing social media scholarly activities and their broad-reaching influence on the mission of education, research, and patient care, but have been slow to acknowledge them as academic currency. The Mayo Clinic is a forerunner in developing a framework for the incorporation of social media scholarship into promotion and tenure criteria.[14] They have established a Social Media Network through which they develop best practices and train physicians and staff.[15] However, there are examples of physicians who do not work in environments that include social media engagement in promotion and tenure criteria, but who individually established metrics of their social media influence and impact, included them as a complement to the traditional requirements that were in their dossier, and leveraged them to a promotion from assistant to associate professors.[16,17] Examples are provided in Table 1.

Take-away points

1. Social media is a useful tool for curation and dissemination of health information.
2. Familiarize yourself with the social media policies of your employer and professional societies' recommendations for professionalism online.
3. Be deliberate about nurturing your social media presence via regularly sharing credible content and engaging other users.
4. Social media can be used effectively to promote the value of your work in clinical care, medical education, research, and/or academic promotion.

Summary

We have outlined why you should consider establishing and maintaining a professional presence on social media and how to accomplish this. You will have a smoother experience if you learn your local rules and policies and abide by our suggestions to avoid adverse outcomes. You will be most effective if you establish goals for your social media participation and revisit these goals over time for continued relevance and success and if you have consistent and valuable output that will support attainment of these goals. Welcome to the GI social media community! Be sure to follow *Clinical Gastroenterology and Hepatology* and the AGA on Facebook (facebook.com/cghjournal and facebook.com/amergastroassn) and Twitter (@AGA_CGH and @AmerGastroAssn), and the coauthors (@DMGrayMD and @DrDeborahFisher) on Twitter.

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(17.5g/3.13g/1.6g) per 6 ounces

*This clinical trial was not included in the product labeling. †Based on investigator grading.

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.

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