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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Courtesy Dr. Mette Wod

Dr. Mette Wod and her coauthors used two large, prospective, population-based studies to study PPI use and later cognitive function.

PPI use not linked to cognitive decline

BY NICK ANDREWS
MDedge News

Use of proton pump inhibitors (PPIs) is not associated with cognitive decline in two prospective, population-based studies of identical twins published in the May issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2018.01.034).

"No stated differences in [mean cognitive] scores between PPI users and nonusers were significant," wrote Mette Wod, PhD, of the University of Southern Denmark, Odense, with her associates.

Past research has yielded mixed findings about whether using PPIs affects the risk of dementia. Preclinical data suggest that exposure to these drugs affects amyloid levels in mice, but "the evidence is equivocal, [and] the results of epidemiologic studies [of humans] have also been inconclusive, with more recent studies pointing toward a null association," the investigators wrote. Furthermore, there are only "scant" data on whether long-term PPI use affects cognitive function, they noted.

To help clarify the issue, they analyzed prospective data from two studies of twins in Denmark: the Study of Middle-Aged Dan-

See **PPI** · *page 6*

Sessile serrated colon polyps may be detectable noninvasively

BY NEIL OSTERWEIL
MDedge News

Sessile serrated polyps (SSPs), notorious for being difficult to detect and for their potential to become malignant colorectal tumors, appear to be caused by a single oncogenic mutation, a finding that could lead to better early detection of some colorectal cancers through noninvasive stool testing, investigators say.

Using a comprehensive battery of genomic testing and DNA methylation profiling, David Jones, PhD, of the Oklahoma Medical Research Foundation in Oklahoma City and his colleagues compared SSPs with familial adenomatous polyps (FAPs), and found that the V600E mutation in BRAF (V-Raf Murine Sarcoma Viral Oncogene Homolog B) was the sole cancer-causing mutation in SSPs.

They also found a distinct DNA methylation pattern unique to SSPs.

"These SSP-specific methylation patterns effectively distinguish SSP from adenomatous polyps, which could be important for both diagnosis and treatment. It also suggests that the BRAF-V600E mutation directly or indirectly results in the remodeling of the epigenome and that this may set a stage for tumor progression," they wrote in the open-access

See **Colon polyps** · *page 16*

H. pylori eradication cuts new gastric cancers by half

BY ANDREW D. BOWSER
MDedge News

Treatment for *Helicobacter pylori* infection cut the incidence of new gastric cancers in half among patients undergoing endoscopic resection of early gastric cancer, according to results of a recent randomized, placebo-controlled study.

Patients receiving *H. pylori* treatment also had greater improvement from baseline in grade of gastric corpus atrophy, compared with patients receiving placebo, according to the

See **Gastric cancers** · *page 16*

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LETTER FROM THE EDITOR: DDW is a celebration of diversity


DR. ALLEN

Digestive Disease Week® (DDW) is approaching rapidly. One might say, with strong justification, that the overarching theme for DDW is a celebration of diversity. We are entering the era of "omics" and current research suggests a microbiome rich in diversity is associated with health, while a less-diverse biome is associated with digestive disorders – inflammatory bowel disease for example. Multiple abstracts and presentations will be related to research into microbiome alterations in disease. In nature, diversity is a key to survival.

Farmers know the value of diversity and the devastating effects of restricted diversity. When fields are restricted to a single crop year after year, artificial fertilizers must be used to restore fertility. Organic farmers understand the need for diversity in the form of crop rotation. No forest can survive for long without rich biological diversity. Even cancer reminds us of the importance of diversity. Restricted diversity in the form of cellular monoclonality is one of the hallmarks of malignant growth.

I spent a morning with Dr. Joel Richter last month and he reminded me that our current surveillance system is failing to impact annual incidence of esophageal adenocarcinoma.

DDW, our annual hallmark meeting, emphasizes our need for diverse thoughts and intellectual discourse as we advance the science of gastroenterology, endoscopy, hepatology, and surgery. Biology does not tolerate restrictions on diversity for long. Diversity makes DDW great.

In this month's issue of *GI & Hepatology News*, we are reassured that PPIs are not linked to cognitive decline. Sessile serrated polyps, often missed at colonoscopy and CT colography might be detected with noninvasive testing as the field of blood-based cancer screening advances. Pay attention to the exciting bleeding-edge technology emerging from the AGA Tech Summit – especially technologies to treat obesity. Read about some of the continuing barriers to CRC screening in underserved populations – if we are to achieve 80% screening rates we must focus on people challenged to access our health care system.

Finally, consider the AGA Clinical Practice Update about Barrett's esophagus. I spent a morning with Joel Richter, MD, last month and he reminded me that our current surveillance system is failing to impact annual incidence of esophageal adenocarcinoma. Perhaps we should focus on a one-time screen for those most at risk, catching prevalent disease at an early stage.

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

DDSEPeight Quick quiz

Q1. Which of the following conditions is associated with unconjugated hyperbilirubinemia and is fatal, if untreated?
A. Dubin Johnson syndrome
B. Crigler-Najjar syndrome type 1
C. Rotor syndrome
D. Crigler-Najjar syndrome type 2
E. Gilbert's syndrome

Q2. A 78-year-old woman presents with anemia and peripheral neuropathy. Laboratory evaluation reveals elevated MCV and vitamin B_{12} deficiency. Antiparietal and anti-intrinsic factor antibodies are positive. Endoscopy reveals atrophic-appearing mucosa and an 8-mm nodule in the gastric body. Complete endoscopic resection of the nodule is performed. What is the most likely finding on pathological examination of the resected lesion?
A. Spindle cells
B. Nests of endocrine cells
C. Smooth muscle proliferation
D. Adenocarcinoma
E. G-cell hyperplasia

The answers are on page 15.

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The AGA Institute headquarters is located at 4930 Del Ray Avenue, Bethesda, MD 20814, ginews@gastro.org.

Editorial Offices 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

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FROM THE AGA JOURNALS

Is this the final answer?

PPI *from page 1*

ish Twins, in which individuals underwent a five-part cognitive battery at baseline and then 10 years later, and the Longitudinal Study of Aging Danish Twins, in which participants underwent the same test at baseline and 2 years later. The cognitive test assessed verbal fluency, forward and backward digit span, and immediate and delayed recall of a 12-item list. Using data from a national prescription registry, the investigators also estimated individuals' PPI exposure starting 2 years before study enrollment.

In the study of middle-aged twins, participants who used high-dose PPIs before study enrollment had cognitive scores that were slightly lower at baseline, compared with PPI nonusers. Mean baseline scores were 43.1 (standard deviation, 13.1) and 46.8 (SD, 10.2), respectively. However, after researchers adjusted for numerous clinical and demographic variables, the between-group difference in baseline scores narrowed to just 0.69 (95% confidence interval, –4.98 to 3.61), which was not statistically significant.

'Cognitive scores of more than 7,800 middle-aged and older Danish twins at baseline did not indicate an association with previous PPI use.'

The longitudinal study of older twins yielded similar results. Individuals who used high doses of PPIs had slightly higher adjusted mean baseline cognitive score than did nonusers, but the difference did not reach statistical significance (0.95; 95% CI, –1.88 to 3.79).

Furthermore, prospective assessments of cognitive decline found no evidence of an effect. In the longitudinal aging study, high-dose PPI users had slightly less cognitive decline (based on a smaller change in test scores over time) than did nonusers, but the adjusted difference in decline between groups was not significant (1.22 points; 95% CI, –3.73 to 1.29). In the middle-aged twin study, individuals with the highest levels of PPI exposure (at least 1,600 daily doses) had slightly less cognitive decline than did nonusers, with an adjusted difference of 0.94 points (95% CI, –1.63 to 3.50) between groups, but this did not reach statistical significance.

"This study is the first to examine the association between long-term PPI use and cognitive decline in a population-based setting," the researchers concluded. "Cognitive scores of more than 7,800 middle-aged and older Danish twins at baseline did not indicate an association with previous PPI use. Follow-up data on more than 4,000 of these twins did not indicate that use of this class of drugs was correlated to cognitive decline."

Odense University Hospital provided partial funding. Dr. Wod had no disclosures. Three coinvestigators disclosed ties to AstraZeneca and Bayer AG.

ginews@gastro.org

SOURCE: Wod M et al. Clin Gastro Hepatol. 2018 Feb 3. doi: 10.1016/j.cgh.2018.01.034.

Over the last 20 years, there have been multiple retrospective studies which have shown associations between the use of proton pump inhibitors (PPIs) and a wide constellation of serious medical complications. However, detecting an association between a drug and a complication does not necessarily indicate that the drug was indeed responsible.

DR. TARGOWNIK

The evidence supporting the assertion that PPIs cause cognitive decline is among the most tenuous of all the PPI/complication associations. The initial reports linking PPI use to dementia emerged in 2016 based on the results of a German retrospective analysis, which showed an association between PPIs and having a health care contact coded as dementia. However, this study had numerous methodological flaws, including the investigators not using a validated definition for dementia and not being able to control for conditions that may be more common in both PPI users and persons with dementia. In addition, there is little reason to believe that PPIs, based on their mechanism of action, should have any negative effect on cognitive function. Nevertheless, this paper was extensively cited in the lay press, and likely led to the inappropriate discontinuation of PPI therapy among persons with ongoing indications, or in the failure to start PPI therapy in persons who would have derived benefit.

This well-done study by Wod et al., which shows no significant association between PPI use and decreased cognition and cognitive decline will, I hope, serve to allay any misplaced concerns that may exist among clinicians and patients about PPI use in this population. This paper has notable strengths, most importantly having access to results of a direct, unbiased assessment of changes in cognitive function over time and accurate assessment of PPI exposure. Short of performing a controlled, prospective trial, we are unlikely to see better evidence indicating a lack of a causal relationship between PPI use and changes in cognitive function. This provides assurance that patients with indications for PPI use can continue to use them.

Laura E. Targownik, MD, MSHS, FRCPC, is section head, section of gastroenterology, University of Manitoba, Winnipeg; Gastroenterology and Endoscopy Site Lead, Health Sciences Centre, Winnipeg; associate director, University of Manitoba Inflammatory Bowel Disease Research Centre; associate professor, department of internal medicine, section of gastroenterology, University of Manitoba. She has no conflicts of interest.

Heavy drinking did not worsen clinical outcomes from drug-induced liver injury

BY AMY KARON
MDedge News

Heavy drinking was not associated with higher proportions of liver-related deaths or liver transplantation among patients with drug-induced liver injury (DILI), according to the results of a prospective multicenter cohort study reported in the May issue of Clinical Gastroenterology and Hepatology (doi: 10.1053/j.gastro.2018.01.062).

Anabolic steroids were the most common cause of DILI among heavy drinkers, defined as men who averaged more than three drinks a day or women who averaged more than two drinks daily, said Lara Dakhoul, MD, of Indiana University, Indianapolis, and her associates. There also was no evidence that heavy alcohol consumption increased the risk of liver injury attributable to isoniazid exposure, the researchers wrote in.

Although consuming alcohol significantly increases the risk of acetaminophen-induced liver injury, there is much less clarity about the relationship between drinking and hepatotoxicity from drugs such as duloxetine or antituberculosis medications, the researchers noted. In fact, one recent study found that drinking led to less severe liver injury among individuals with DILI. To better elucidate these links, the investigators studied 1,198 individuals with confirmed or probable

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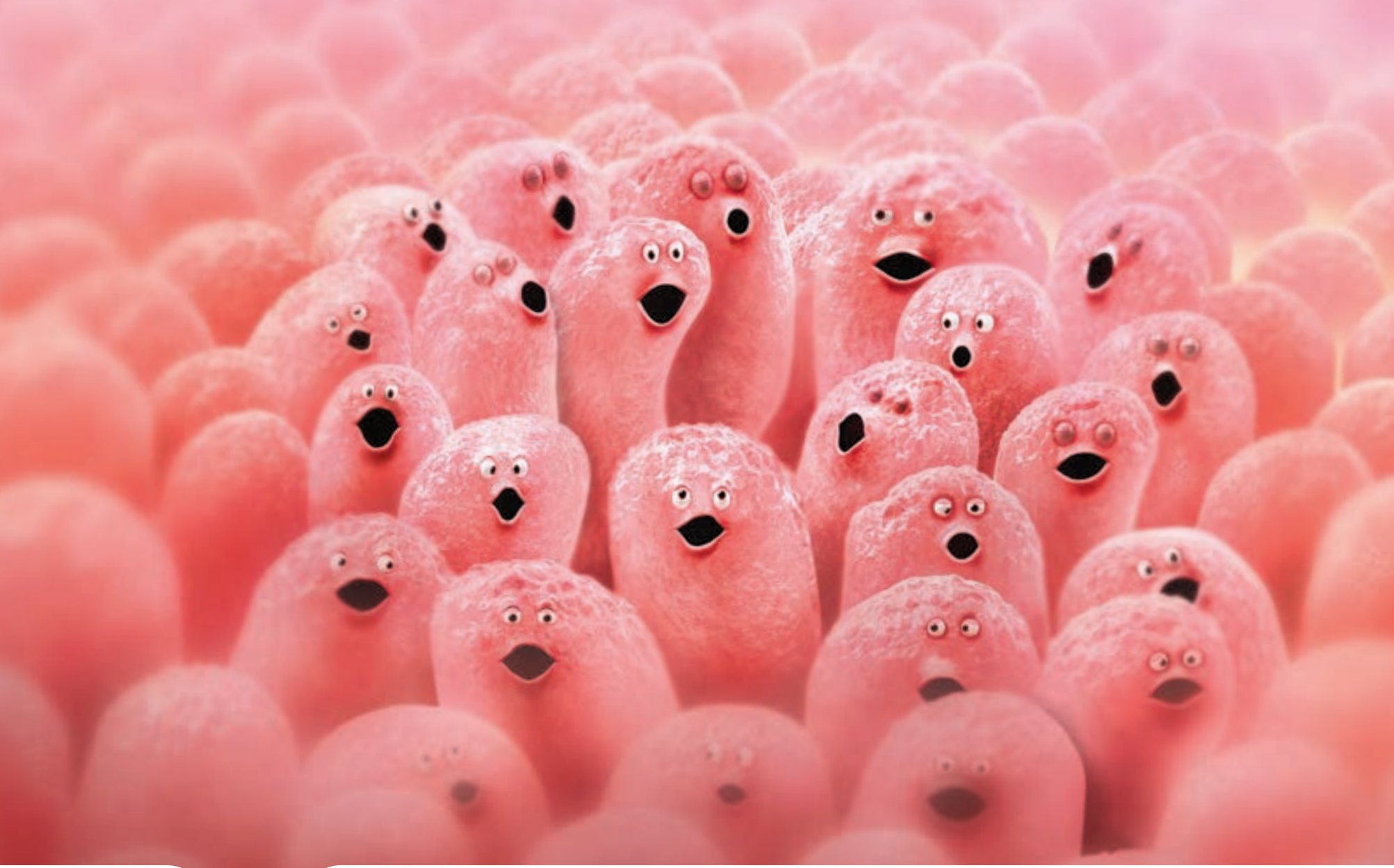

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*In a study where 412 longitudinal serum samples from 118 adult Crohn's disease (CD) patients were collected at the time or close to endoscopy. Endoscopic scoring was centrally read and mucosal healing was defined as the absence of visual endoscopic ulcers.

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References: 1. Vermeire S, D'Haens G, Hale M, et al. A novel serum test to describe the mucosal healing state by disease location in Crohn's disease patients. Presented at: World Congress of Gastroenterology; October 13-18, 2017; Orlando, FL. **2.** Kelly OB, Silverberg MS, Dulai PD, et al. Development and validation of a multi-marker serum test for the assessment of mucosal healing in Crohn's disease patients. Presented at: World Congress of Gastroenterology; October 13-18, 2017; Orlando, FL.

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FROM THE AGA JOURNALS

One in seven Americans has fecal incontinence

BY AMY KARON
MDedge News

One in seven respondents to a national survey reported a history of fecal incontinence, including one-third within the preceding week, investigators reported.

"Fecal incontinence [FI] is age-related and more prevalent among individuals with inflammatory bowel disease, celiac disease, irritable bowel syndrome, or diabetes than people without these disorders. Proactive screening for FI among these groups is warranted," Stacy B. Menees, MD, and her associates wrote in the May issue of Gastroenterology (doi: 10.1053/j.gastro.2018.01.062).

Accurately determining the prevalence of FI is difficult because patients are reluctant to disclose symptoms and physicians often do not ask. In one study of HMO enrollees, about a third of patients had a history of FI but fewer than 3% had a medical diagnosis. In other studies, the prevalence of FI has ranged from 2% to 21%. Population aging fuels the need to narrow these estimates because FI becomes more common with age, the investigators noted.

Accordingly, in October 2015, they used a mobile app called MyGIHealth to survey nearly 72,000 individuals about fecal incontinence and other GI symptoms. The survey took about 15 minutes to complete, in return for which respondents could receive cash, shop online, or donate to charity. The investigators assessed FI severity by analyzing responses to the National Institutes of Health

Continued on following page

Fecal incontinence (FI) is a common problem associated with significant social anxiety and decreased quality of life for patients who experience it. Unfortunately, patients are not always forthcoming regarding their symptoms, and physicians often fail to inquire directly about incontinence symptoms.


DR. MCABEE

Previous studies have shown the prevalence of FI to vary widely across different populations. Using novel technology through a mobile app, researchers at the University of Michigan, Ann Arbor, and Cedars-Sinai Medical Center, Los Angeles, have been able to perform the largest population-based study of community-dwelling Americans. They confirmed that FI is indeed a common problem experienced across the spectrum of age, sex, race, and socioeconomic status and interferes with the daily activities of more than one-third of those who experience it.

This study supports previous findings of an age-related increase in FI, with the highest prevalence in patients over age 65 years. Interestingly, males were more likely than females to have experienced FI within the past week, but not more likely to have ever experienced FI. While FI is often thought of as a primarily female problem (related to past obstetrical injury), it is important to remember that it likely affects both sexes equally.

Other significant risk factors include diabetes and gastrointestinal disorders. This study also confirms prior population-based findings that patients with chronic constipation are more likely to suffer FI. Finally, this study also identified risk factors associated with FI symptom severity including diabetes, HIV/AIDS, Crohn's disease, celiac disease, and chronic constipation. This is also the first study to show differences between racial/ethnic groups, suggesting higher FI symptom scores in Latinos and African Americans.

The strengths of this study include its size and the anonymity provided by an internet-based survey regarding a potentially embarrassing topic; however, it also may have led to the potential exclusion of older individuals or those without regular internet access.

In summary, I believe this is an important study which confirms that FI is common among Americans while helping to identify potential risk factors for the presence and severity of FI. I am hopeful that with increased awareness, health care providers will become more prudent in screening their patients for FI, particularly in these higher-risk populations.

Stephanie A. McAbee, MD, is an assistant professor of medicine in the division of gastroenterology, hepatology, and nutrition at Vanderbilt University Medical Center, Nashville, Tenn. She has no conflicts of interest.

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DILI who enrolled in the DILI Network study (DILIN) between 2004 and 2016. At enrollment, all participants were asked if they consumed alcohol, and those who reported drinking within the past 12 months were offered a shortened version of the Skinner Alcohol Dependence Scale to collect details on alcohol consumption, including type, amount, and frequency.

In all, 601 persons reported consuming at least one alcoholic drink in the preceding year, of whom 348 completed the Skinner questionnaire. A total of 80 individuals reported heavy alcohol consumption. Heavy drinkers were typically in their early 40s, while nondrinkers tended to be nearly 50 years old (*P* less than .01). Heavy drinkers were also more often men (63%) while nondrinkers were usually women (65%; *P* less than .01). Heavy drinkers were significantly more likely to have DILI secondary to anabolic steroid exposure (13%) than were nondrinkers (2%; *P* less than .001). However, latency, pattern of liver injury, peak enzyme levels, and patterns of recovery from steroid hepatotoxicity were similar regardless of alcohol history.

A total of eight patients with DILI died of liver-related causes or underwent liver transplantation, and proportions of patients with these outcomes were similar regardless of alcohol history. These eight patients had no evidence of hepatitis C virus infection, but three appeared to have underlying alcoholic liver disease with superimposed acute-on-chronic liver failure. Heavy drinkers did not have significantly higher DILI severity scores than nondrinkers, but they did have significantly higher peak serum levels of alanine aminotransferase (1,323 U/L vs. 754, respectively; *P* = .02) and significantly higher levels of bilirubin (16.1 vs. 12.7 mg/dL; *P* = .03).

Heavy drinkers were significantly more likely to have DILI secondary to anabolic steroid exposure (13%) than were nondrinkers (2%; *P* less than .001).

The two fatal cases of DILI among heavy drinkers involved a 44-year-old man with underlying alcoholic cirrhosis and steatohepatitis who developed acute-on-chronic liver failure 11 days after starting niacin, and a 76-year-old man with chronic obstructive pulmonary disease and bronchitis flare who developed severe liver injury and skin rash 6 days after starting azithromycin.

The study was not able to assess whether heavy alcohol consumption contributed to liver injury from specific agents, the researchers said. Additionally, a substantial number of drinkers did not complete the Skinner questionnaire, and those who did might have underestimated or underreported their own alcohol consumption. "Counterbalancing these issues are the [study's] unique strengths, such as prospective design, larger sample size, well-characterized DILI phenotype, and careful, structured adjudication of causality and severity," the researchers wrote.

Funders included the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute. Dr. Dakhoul had no conflicts of interest. One coinvestigator disclosed ties to numerous pharmaceutical companies.

ginews@gastro.org

SOURCE: Dakhoul L et al. Clin Gastro Hepatol. 2018 Jan 3. doi: 10.1016/j.cgh.2017.12.036.

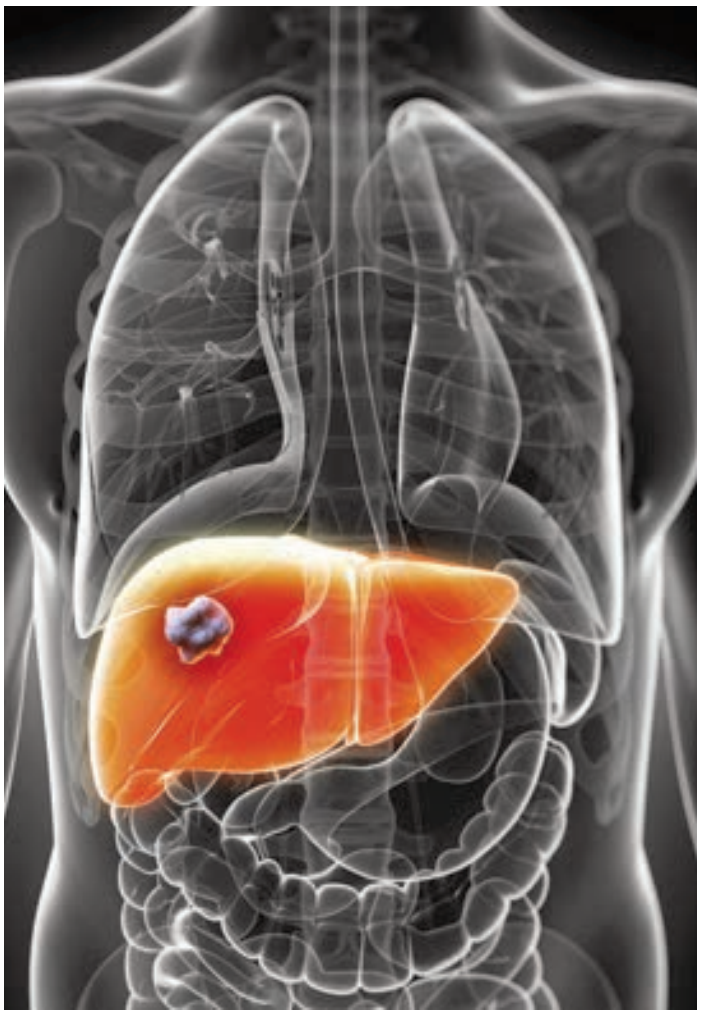
FROM THE AGA JOURNALS

Alpha fetoprotein boosted detection of liver cancer

BY AMY KARON
MDedge News

For patients with cirrhosis, adding serum alpha fetoprotein testing to ultrasound significantly boosted its ability to detect early-stage hepatocellular carcinoma, according to the results of a systematic review and meta-analysis reported in the May issue of Gastroenterology (doi: 10.1053/j.gastro.2018.01.064).

Used alone, ultrasound detected only 45% of early-stage hepatocellular carcinomas (95% confidence interval, 30%-62%), reported Kristina Tzartzeva, MD, of the University of Texas, Dallas, with her associates. Adding alpha fetoprotein (AFP) increased this sensitivity to 63% (95% CI, 48%-75%; *P* = .002). Few studies evaluated alternative surveillance tools, such as CT or MRI.



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Diagnosing liver cancer early is key to survival and thus is a central issue in cirrhosis management. However, the best surveillance strategy remains uncertain, hinging as it does on sensitivity, specificity, and cost. The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend that cirrhotic patients undergo twice-yearly ultrasound to screen for hepatocellular carcinoma (HCC), but they disagree about the value of adding serum biomarker AFP testing. Meanwhile, more and more clinics are using CT and MRI because of concerns about the unreliability of ultrasound. "Given few direct comparative studies, we are forced to primarily rely on indirect comparisons across studies," the reviewers wrote.

To do so, they searched MEDLINE and Scopus and identified 32 studies of HCC surveillance that comprised 13,367 patients, nearly all with baseline cirrhosis. The studies were published from 1990 to August 2016.

Ultrasound detected HCC of any stage with a sensitivity of 84% (95% CI, 76%-92%), but its sensitivity for detecting early-stage disease was less than 50%. In studies that performed direct comparisons, ultrasound alone was significantly less sensitive than ultrasound plus AFP for detecting all stages of HCC (relative risk, 0.80; 95% CI, 0.72-0.88) and early-stage disease (0.78; 0.66-0.92). However, ultrasound alone was more specific than ultrasound plus AFP (RR, 1.08; 95% CI, 1.05-1.09).

Four studies of about 900 patients evaluated cross-sectional imaging with CT or MRI. In one single-center, randomized trial, CT had a sensitivity of 63% for detecting early-stage disease, but the 95% CI for this estimate was very wide (30%-87%) and CT did not significantly outperform ultrasound (Aliment Pharmacol Ther. 2013;38:303-12). In another study, MRI and ultrasound had significantly different sensitivities of 84% and 26% for detecting (usually) early-stage disease (JAMA Oncol. 2017;3[4]:456-63).

'Using ultrasound in combination with AFP appears to significantly improve sensitivity for detecting early HCC with a small, albeit statistically significant, trade-off in specificity. There are currently insufficient data to support routine use of CT- or MRI-based surveillance in all patients with cirrhosis.'

"Ultrasound currently forms the backbone of professional society recommendations for HCC surveillance; however, our meta-analysis highlights its suboptimal sensitivity for detection of hepatocellular carcinoma at an early stage. Using ultrasound in combination with AFP appears to significantly improve sensitivity for detecting early HCC with a small, albeit statistically significant, trade-off in specificity. There are currently insufficient data to support routine use of CT- or MRI-based surveillance in all patients with cirrhosis," the reviewers concluded.

The National Cancer Institute and Cancer Prevention Research Institute of Texas provided funding. None of the reviewers had conflicts of interest.

ginews@gastro.org

SOURCE: Tzartzeva K et al. Gastroenterology. 2018 Feb 6. doi: 10.1053/j.gastro.2018.01.064.

Continued from previous page

FI Patient Reported Outcomes Measurement Information System questionnaire.

Of the 10,033 respondents reporting a history of fecal incontinence (14.4%), 33.3% had experienced at least one episode in the past week. About a third of individuals with FI said it interfered with their daily activities. "Increasing age and concomitant diarrhea and constipation were associated with increased odds [of] FI," the researchers wrote. Compared with individuals aged 18-24 years, the odds of having ever experienced FI rose by 29% among those aged 25-45 years, by 72% among those aged 45-64 years, and by 118% among persons aged 65 years and older.

Self-reported FI also was significantly more common among individuals with Crohn's disease (41%), ulcerative colitis (37%), celiac disease (34%), irritable bowel syndrome (13%), or diabetes (13%) than it was among persons without these conditions. Corresponding odds ratios ranged from about 1.5 (diabetes) to 2.8 (celiac disease).

For individuals reporting FI within the past week, greater severity (based on their responses to the NIH FI Patient Reported Outcomes Measurement Information System questionnaire) significantly correlated with being non-Hispanic black (*P* = .03) or Latino (*P* = .02) and with having Crohn's disease (*P* less than .001), celiac disease (*P* less than .001), diabetes (*P* = .04), human immunodeficiency syndrome (*P* = .001), or chronic idiopathic constipation (*P* less than .001). "Our study is the first to find differences among racial/ethnic groups regarding FI severity," the researchers noted. They did not speculate on reasons for the finding, but stressed the importance of screening for FI and screening patients with FI for serious GI diseases.

Ironwood Pharmaceuticals funded the National GI Survey, but the investigators received no funding for this study. Three coinvestigators reported ties to Ironwood Pharmaceuticals and My Total Health.

ginews@gastro.org

SOURCE: Menees SB et al. Gastroenterology. 2018 Feb 3. doi: 10.1053/j.gastro.2018.01.062.

Life and health are not consistent across the U.S.

BY ANDREW D. BOWSER
MDedge News

While U.S. death rates have declined overall, marked geographic disparities exist at the state level in burden of disease, injuries, and risk factors, according to a comprehensive analysis.

Life expectancy varies substantially, for example, ranging from a high of 81.3 years in Hawaii to a low of 74.7 years in Mississippi, according to results from the analysis of data from the Global Burden of Disease (GBD) study (JAMA. 2018;319[14]:1444-72).

Previously decreasing death rates for adults have reversed in 19 states, according to the analysis, which covers the years 1990-2016.

Hardest hit were Kentucky, New Mexico, Oklahoma, West Virginia, and Wyoming, which had mortality increases of more than 10% among adults aged 20-55 years. Those increases were largely due to causes such as substance use disorders, self-harm, and cirrhosis, according to the U.S. Burden of Disease Collaborators, who authored the report.

"These findings should be used to examine the causes of health variations and to plan, develop, and implement programs and policies to improve health overall and eliminate disparities in the United States," the authors wrote.

Overall, U.S. death rates have declined from 745.2 per 100,000 persons in 1990 to 578.0 per 100,000 persons in 2016, according to the report.

Likewise, health outcomes throughout the United States have improved over time for some conditions, such as ischemic heart disease, lung cancer, and neonatal preterm complications, the report says.

However, those gains are offset by rising death rates due to drug use disorders, chronic kidney disease, cirrhosis, chronic obstructive pulmonary disease, hypertension, and self-harm.

Opioid use disorders have become increasingly prevalent, moving from the 11th leading cause of disability-adjusted life- years in 1990 to the 7th in 2016, a 74.5% change, according to investigators.

The three most important risk factors in the United States are high body mass index, smoking, and high fasting plasma glucose, the analysis showed. Of those risk factors, only smoking is decreasing, authors noted.

Many risk factors contributing to disparities in burden among states are amenable to medical treatment that emphasizes supportive behavioral and lifestyle changes, according to the authors.

"Expanding health coverage for certain conditions and medications should be considered and adopted to reduce burden," they said.

Substance abuse disorders, cirrhosis, and self-harm, the causes of the mortality reversal in Kentucky, New Mexico, and other states, could be addressed via a wide range of interventions, according to the investigators.

Prevention programs could address the root causes of substance use and causes of relapse, while physicians can play a "major role" in addiction control through counseling of patients on pain control medication, they said.

Interventions to treat hepatitis C and decrease excessive alcohol consumption could help address cirrhosis, while for self-harm, the most promising approaches focus on restricting access to lethal means, they said, noting that a large proportion of U.S. suicides are due to firearms.

"While multiple strategies are available for dealing with these problems, they have not until very recently garnered attention," investigators wrote.

The study was supported in part by the National Institute of Environmental Health Sciences and the Bill and Melinda Gates Foundation. Some individual study collaborators reported disclosures related to Savient, Takeda, Crealta/Horizon, Regeneron, Allergan, and others.

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SOURCE: The U.S. Burden of Disease Collaborators. JAMA. 2018;319(14):1444-72.

PERSPECTIVE

Findings should motivate clinicians and policy makers

This report on Global Burden of Disease (GBD) study data profoundly and powerfully illuminates U.S. health trends over time and by geography. There is much unfinished business for us, nationally and at the state level.

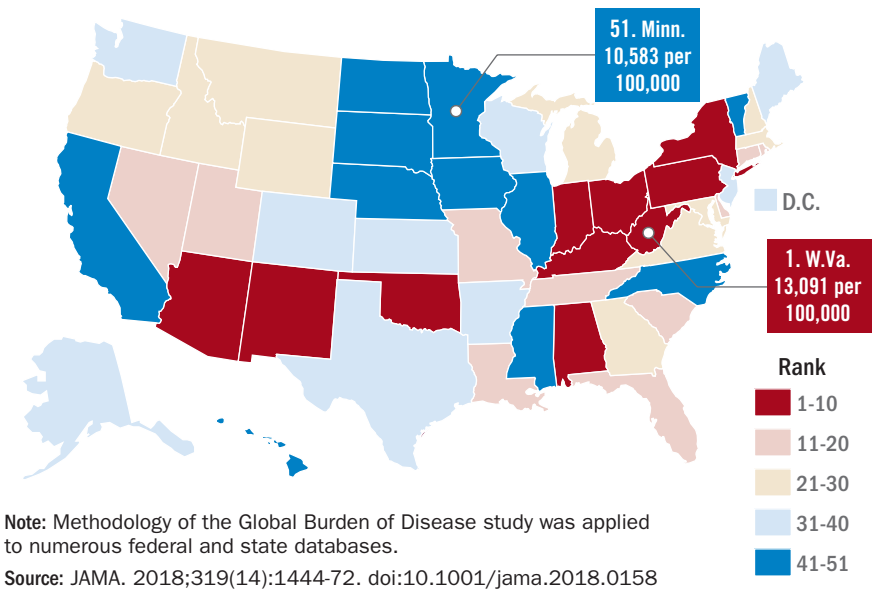
Clinicians and policy makers can use the rankings to evaluate why many individuals are still experiencing injury, disease, and deaths that are preventable; in doing so, the entire nation could more closely resemble a United States of health.

Clinicians could use the results to help guide patients through evidence-based disease prevention and early intervention, a strategy that has led to decreases in death due to cancer and cardiovascular disease over the past few decades.

At the same time, policy makers could use GBD 2016 results to reevaluate current national attitudes toward disease prevention.

Howard K. Koh, MD, MPH, is with the Harvard T.H. Chan School of Public Health, Boston. Anand K. Parekh, MD, MPH, is with the Bipartisan Policy Center in Washington. The comments above are derived from an editorial accompanying the report from the U.S. Burden of Disease Collaborators (JAMA. 2018;319[14]:1438-40). Dr. Koh and Dr. Parekh reported no conflicts of interest related to the editorial.

Years lived with disability per 100,000 population, 2016



Note: Methodology of the Global Burden of Disease study was applied to numerous federal and state databases.

Source: JAMA. 2018;319(14):1444-72. doi:10.1001/jama.2018.0158

MDedge News

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Medicare Part D plans get flexibility to make changes

BY GREGORY TWACHTMAN
MDedge News

Medicare Part D prescription drug plan sponsors will have flexibility to make maintenance changes to their formularies in 2019 as part of a broader effort to lower costs for Part D enrollees.

These so-called "maintenance changes" to a formulary can now be made prior to receiving approval from the Centers for Medicare & Medicaid Services after the agency finalized a proposal in a rule updating regulations governing Medicare Part D and Medicare Advantage.

CMS generally approves maintenance changes, such as removing a brand-name drug and substituting a generic equivalent when it is approved or after the publication of new clinical guidelines, or when a plan moves a drug to a higher tier or adds prior authorization to it; in the past there were delays associated with the change.

The new rule allows plans to make formulary changes immediately upon generic approval assuming certain requirements are met, including generally advising Part D plan members beforehand that changes can occur without a specific advance notice and later providing information about any specific generic substitutions that occur.

CMS noted that the proposed changes drew concerns, particularly regarding changes that could be made without giving patients a chance to discuss them with their doctors about transitioning to a new medication and other concerns. However, the rule states that the policy "strikes the right balance between providing beneficiaries with access to needed drugs and Part D sponsors with flexibility to administer plans."

Another area in the rule that CMS expects will generate savings is a new policy on biosimilars that affects beneficiaries receiving low-income subsidy benefits. Going forward, the agency will treat biosimilars and interchangeable biological products the same as generics in terms of determining copays for low-income subsidy enrollees.

Other changes in the rule eliminate requirements that sponsors eliminate plan offerings unless they "meaningfully differ" from one another, allowing plans to offer more choices to beneficiaries, and potentially more cost-saving options to meet their needs. It also clarifies rules regarding the "any willing provider" requirement to allow for more pharmacy options available to Part D enrollees and allow them to shop for best deals for their pharmaceuticals.

In combination with the final 2019 call letter that provides Medicare Advantage and Part D sponsors with the guidelines for submitting their plan designs for the coming coverage year, the rule also finalizes policies related to stemming the opioid crisis, including providing tools to help prevent opioid overprescribing and abuse. The rule implements provisions of the Comprehensive Addiction and Recovery Act of 2016 that require CMS to supply a framework that allows Part D sponsors to implement drug management programs to limit at-risk beneficiaries' access to coverage for frequently abused drugs.

KENISHIROTIE/THINKSTOCK

gtwachtman@mdedge.com

Include pregnant women in clinical trials: FDA considers how

BY RANDY DOTINGA
MDedge News

Pregnant women are rarely included in clinical drug trials, creating a significant and potentially dangerous gap in knowledge. Now, a new draft guidance from the Food and Drug Administration broadens the discussion about these trials, suggesting issues to consider – including ethics and risks – when testing medications in pregnant women.

"The guidance opens the possibility of ethical conduct of trials in pregnant women but carefully lays out the caveats to be considered," Christina Chambers, PhD, a perinatal epidemiologist at the University of California, San Diego, said in an interview. "With proper planning and thoughtful consultation with the relevant experts, this change in regulatory limitations will benefit pregnant women and their children."

As Dr. Chambers noted, "we have very limited pregnancy safety data for most prescription drugs" because of the lack of clinical trials and comprehensive postmarketing studies in this population.

Attitudes have evolved toward more acceptance of including pregnant women in drug trials, according to a 2015 committee opinion from the American College of Obstetricians and Gynecologists. Still, "concerns about the potential for pregnancy in research trial participants have led to practices involving overly burdensome contraception requirements," the opinion states. "Although changes have been made to encourage and recruit more women into research studies, a gap still exists in the available data on health and disease in women, including those who are pregnant" (Obstet Gynecol. 2015;126:e100-7).

The draft guidance, released April 6 by the FDA, is "intended to advance scientific research in pregnant women, and discusses issues that should be considered within the framework of human subject protection regulations," according to posting comments in the Federal Register.

The draft notes that in some cases, the lack of data about drugs may harm pregnant women and their fetuses by leading physicians to be fearful about prescribing medication. Conversely, physicians and pregnant women are often in the dark about the risks and benefits of medications that are prescribed and used, according to the draft.

In terms of research going forward, the guidance says "development of accessible treatment options for the pregnant population is a significant public health issue."

The guidance, which recommends that clinical trial sponsors consider enlisting ethicists to take part in drug development program, offers these guidelines, among others, to drugmakers:

- It is "ethically justifiable" to include pregnant women in clinical trials under specific circumstances. "Sponsors should consider meeting with the appropriate FDA review division early in the development phase to discuss when and how to include pregnant women in the drug development plan. These discussions should involve FDA experts in bioethics and maternal health."
- "Pregnant women can be enrolled in clinical trials that involve greater than minimal risk to the fetuses if the trials offer the potential for direct clinical benefit to the enrolled pregnant women and/or their fetuses."
- A new pregnancy during a randomized, blinded clinical trial should prompt unblinding "so that counseling may be offered based on whether the fetus has been exposed to the investigational drug, placebo, or control."
- The pregnant woman may continue the trial if potential benefits outweigh the risks.
- In general, pregnant women should not be enrolled in phase 1 and phase 2 clinical trials. Instead, those trials should be completed first "in a nonpregnant population that include females of reproductive potential."
- Several types of events may call for the cessation of a clinical trial that includes pregnant women, such as serious maternal or fetal adverse events.

The draft guidance should take note of the fact that birth defects often don't appear for months or even longer, according to Gerald Briggs, BPharm, FCCP, clinical professor of pharmacy at the University of California, San Francisco. "Until first year of life or later, the babies need to be monitored," he said in an interview.

Mr. Briggs, who led a 2015 report examining the role of pregnant women in phase 4 clinical drug trials, added that the document should take note of recommendations from clinical teratologists regarding the design of animal studies that should be performed prior to human trials (Am J Obstet Gynecol. 2015;213[6]:810-5).

Comments on the draft guidance can be made at www.federalregister.gov and are due by June 8, 2018.

Dr. Chambers and Mr. Briggs reported no relevant disclosures.

ginews@gastro.org

AGA seeks regulatory relief for gastroenterologists

A top priority for AGA this year is to call on the Centers for Medicare & Medicaid Services (CMS), other payors, and Congress to alleviate some of the regulatory burden that currently falls on physicians. Reevaluating prior authorization, step therapy, and Stark reform would allow physicians to devote more time and resources to provide high-quality care. A more comprehensive breakdown of the following key areas is available along with other top issues.

Prior authorization

- AGA urges payors to standardize prior authorization requirements and criteria and make them transparent and easily accessible. The services subject to prior authorization vary by payor, including CMS, as well as by plan type within a given payor. Physicians and physician practices are forced to comply with an increasing and unmanageable number of prior authorization requirements.
- AGA urges payors, including CMS, to develop and implement processes that allow for true "peer-to-peer" dialogues. Gastroenterologists seeking prior authorization for prescription drug or biologic therapy on behalf of a patient should be routed to a physician specialist in the same or similar discipline with expertise in the given condition to discuss the request.

Step therapy

- Step therapy, also known as "fail first," occurs when an insurer requires patients to try and fail one or more lower-cost prescription drug or biologic therapies before covering the therapy originally prescribed by their health care provider.
- AGA urges insurers to reduce the burden of step therapy on physicians and physician practice. AGA supports The Restoring the Patient's Voice Act (H.R. 2077), legislation introduced by Rep. Brad Wenstrup, R-Ohio, and Rep. Raul Ruiz, D-Calif., both physicians, that would provide a clear and timely appeals process when a patient has been subjected to step therapy.

Stark reform

- Stark self-referral laws prohibit physicians from referring patients to an entity in which they have a financial interest, which limits their ability to participate in many advanced alternative payment models (APMs). These prohibitions stifle care delivery innovation by inhibiting practices from incentivizing their physicians to deliver patient care more efficiently, because the practices cannot use resources from designated health services in rewarding or penalizing adherence to new clinical care pathways.
- AGA supports S. 2051/H.R. 4206, the Medicare Care Coordination Improvement Act, which would provide CMS with the regulatory authority to create exceptions under the Stark law for APMs and to remove barriers in the current law to the development and operation of such arrangements.

Gastroenterologists seeking prior authorization for drug or biologic therapy on behalf of a patient should be routed to a physician specialist expert in the given condition to discuss the request.

ginews@gastro.org

Federal spending agreement includes wins for AGA

President Trump signed a $1.3 trillion omnibus appropriations package that includes notable increases for the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) last week. This funding and language is a major victory for digestive disease research and patients. AGA thanks everyone who joined our call to Congress to increase funding for research. Your advocacy matters and makes a difference!

NIH

NIH is a big winner in the omnibus and will receive $37.1 billion for fiscal year 2018, an 8.8% increase over the previous year's funding, which represents the largest increase for NIH since the doubling period over a decade ago.

The omnibus also includes language pushed by AGA to require NIH to provide Congress with an update on the implementation of the recommendations of the National Commission on Digestive Diseases. AGA applauds Congress for including language that will help increase digestive disease research.

Congress also included funding for young researchers and continues to take action to reduce the average age of a new NIH-supported investigator. AGA appreciates the appropriators including this language, which has been a longstanding priority of AGA in supporting young investigators and ensuring that our best and brightest scientists have the support and funding that they need to start their careers.

Language was also included that prohibits the administration from capping administrative and facility fees paid to research institutions.

The All of Us Precision Medicine initiative received an increase of $60 million and antibiotic resistance initiatives received an increase of $50 million.

Opioid funding

The bill includes $4.65 billion to address the opioid epidemic across various government agencies. NIH would receive $1 billion to research opioid addiction and alternative pain management and treatment.

CDC

The CDC would receive $8.3 billion in funding, rejecting President Trump's call for $900 million in cuts.

ginews@gastro.org

Save the date for the 2019 Crohn's & Colitis Congress

Building on the success of this year's inaugural Crohn's & Colitis Congress™, the Crohn's & Colitis Foundation and the American Gastroenterological Association (AGA) are pleased to announce the second annual Crohn's & Colitis Congress. Be sure to save the date:

Feb. 7-9, 2019, at the Bellagio in Las Vegas

The Crohn's & Colitis Congress is the must-attend meeting for all inflammatory bowel disease (IBD) professionals. It offers a bold, multidisciplinary approach to learning in the IBD space as one care team. All health care professionals and research investigators interested in IBD are invited to attend.

By bringing all audiences together to learn from each other, the Congress embodies how IBD research and patient care needs to be approached – it is not "one-size-fits-all" and it requires collaboration from a variety of health practitioners.

By attending the Crohn's & Colitis Congress, attendees will:

- Build a powerful network and share solutions with IBD thought leaders.
- Discover cutting-edge basic, translational and clinical research in the IBD space.
- Determine best practices at every stage of the patient's disease journey.
- Explore new technologies and products from IBD-related exhibitors.
- Earn CME and MOC points.
- Improve skills and patient outcomes.
- Learn together as one multidisciplinary care team.

Get ready to expand your knowledge, network with IBD leaders, and be inspired. Stay tuned at www.crohnscolitiscongress.org for more details coming in later this spring.

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AGA leaders recognized for their contributions to the field

We are proud to announce the 2018 AGA Recognition Award recipients who are honored for their outstanding contributions to the field of gastroenterology and hepatology. The recipients will be formally recognized during Digestive Disease Week® (DDW) 2018 in Washington, D.C., but you can congratulate your colleagues now in the AGA Community.

2018 Recognition Award Recipients

Julius Friedenwald Medal
Loren A. Laine, MD

Distinguished Achievement Award in Basic Science
T. Jake Liang, MD, AGAF

William Beaumont Prize in Gastroenterology
Mary K. Estes, PhD, AGAF

Distinguished Educator Award
James D. Lewis, MD, MSCE, AGAF

Distinguished Clinician Award
Private Practice: Bertha (Nice') E. Toriz, MD

Clinical Academic Practice: Michael L. Kochman, MD, AGAF

Distinguished Mentor Award
Mary K. Estes, PhD, AGAF

Young Investigator Awards
Clinical Science: David S. Goldberg, MD, MSCE

Basic Science: Andrew D. Rhim, MD

You can read more about each award recipient and the awards themselves at gastro.org/about/awards.

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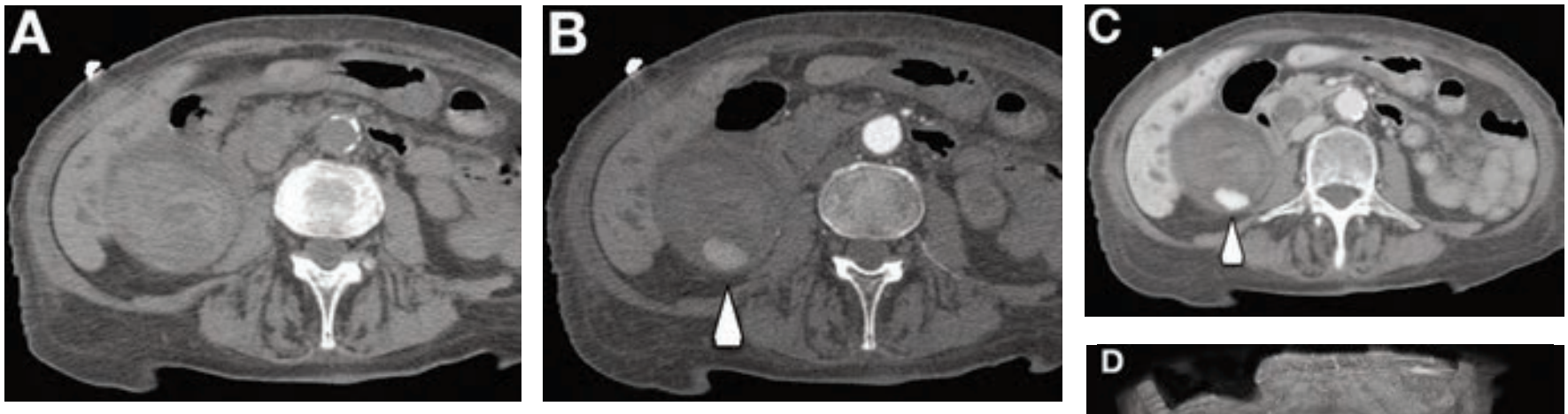
CLINICAL CHALLENGES AND IMAGES



AGA Institute

What is your diagnosis?

By Umberto G. Rossi, MD, Paolo Rigamonti, MD, and Maurizio Cariati, MD. Published previously in Gastroenterology (2016;151[1]e14-5).

An 82-year-old woman arrived in our emergency department for acute right upper abdominal pain with no trauma history. She had a medical history of cardiac arrhythmia (atrial fibrillation) with pacemaker insertion and anticoagulant therapy (warfarin 2.5 mg/d). At the time of her presentation prothrombin time was 36.8 sec, prothrombin activity was 21%, international normalized ratio was 3.32, and platelet count was normal (247 × 10^3/microL). There was no alteration in liver function tests.

She underwent abdominal multiphasic contrast-enhanced multidetector computed tomography. The unenhanced phase demonstrated a distended gallbladder with slightly hyperdense heterogeneous material occupying all its lumen (Figure A). On the arterial phase (Figure B, arrowhead) it appeared inside the lumen of the gallbladder at the middle third of the inferior wall, a focal contrast media area, which become more evident on venous phase (Figure C, D, arrowhead).

After multidisciplinary discussion and correction of coagulation parameters, the patient underwent laparoscopic cholecystectomy.

The diagnosis is on page 26.

DDSEPeight

Quick quiz answers

Q1. Correct Answer: B

Rationale

Gilbert's syndrome and Crigler Najjar syndrome are associated with unconjugated hyperbilirubinemia, whereas Dubin Johnson and Rotor's syndrome are associated with conjugated hyperbilirubinemia. Gilbert's syndrome is common with a variable inheritance pattern (autosomal recessive or dominant) with mild unconjugated hyperbilirubinemia. The cause is an abnormality in the gene UGT1A1 that encodes bilirubin UDPglucuronotransferase. Crigler-Najjar syndrome is a rare autosomal recessive condition resulting from structural mutations or deletions in the UGT1A1 gene leading to failure of bilirubin glucuronidation. Crigler-Najjar syndrome type 1 variant is the complete absence of functional protein. Individuals with this variant have marked unconjugated hyperbilirubinemia from birth and are at risk of kernicterus with bilirubin encephalopathy, and if untreated, they die of neurological complications. Crigler-Najjar syndrome type 2 is the milder variant.

Reference

1. Bosma PJ. Inherited disorders of bilirubin metabolism. J Hepatol. 2003 Jan;38(1):107-17.

Q2. Correct Answer: B

Rationale

This patient has a neuroendocrine tumor (e.g., carcinoid). These tumors are derived from enterochromaffin-like cells and appear as nests or ribbons of endocrine cells. There are three types of carcinoids. Type 1 is the most common and has a benign course: these can be multifocal, well differentiated and associated with type A chronic atrophic gastritis. Small tumors can be treated with endoscopic resection. Type 2 lesions tend to be multifocal and associated with Zollinger-Ellison syndrome and multiple endocrine neoplasia 1. Up to 30% of type 2 tumors present with lymph node metastases. Type 3 gastric carcinoids are not associated with hypergastrinemia and have poor prognosis – they should be managed with surgery.

References

1. ASGE Standards of Practice Committee et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc. 2015;82(1):1-8.
2. Shaib YH et al. Management of gastric polyps: an endoscopy-based approach. Clin Gastroenterol Hepatol. 2013;11(11):1374-84.

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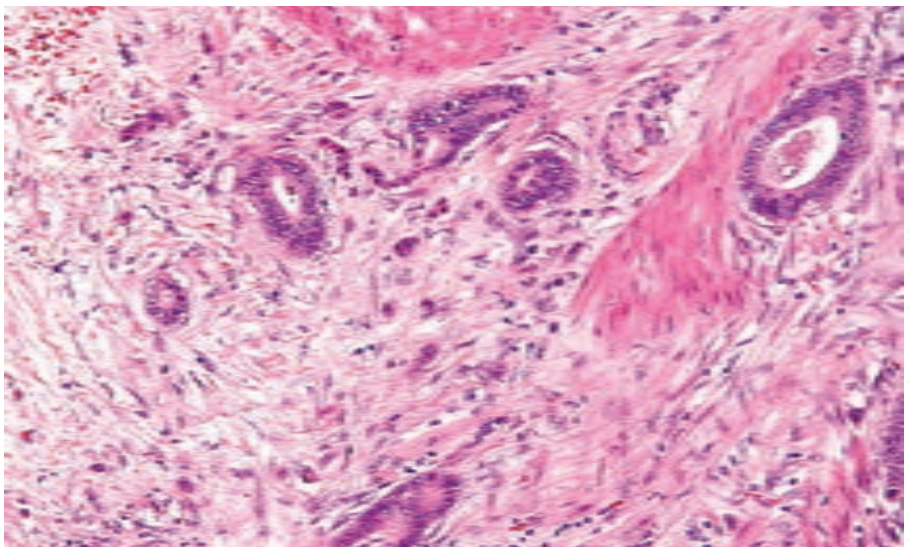
Genetic tests singled out SSPs

Colon polyps *from page 1*



Courtesy Wikimedia Commons/Nephron/Creative Commons

Tumor budding in colorectal carcinoma is shown under magnification.

journal PLOS One.

Approximately one-third of sporadic colorectal cancers, which account for about 95% of all colorectal malignancies, are thought to arise from premalignant serrated lesions, including SSPs, hyperplastic polyps, and traditional serrated adenomas, the authors noted.

Although SSPs and traditional serrated adenomas both have significant potential for malignant transformation, SSPs are much more common, making them important targets for research, diagnosis, and possible interventions.

"Previous surveys of cancer-associated mutations in SSP samples, through targeted analysis of limited known mutations, identified the BRAF-V600E as the key mutation in this disease. However, it is not clear whether other mutations in the same samples contribute to the etiology of this disease," Dr. Jones and his associates wrote.

To better understand both the inherited (genetic) and acquired (epigenetic) basis for SSP and tumor development, the investigators used whole-exome sequencing, genomewide mutation detection, and DNA methylation profiling on multiple samples of both SSPs and FAPs.

They performed exome sequencing on DNA extracted from SSP samples from six patients diagnosed with typical SSP-type colon polyps via colonoscopy and pathology. The samples included one each from five patients and three taken from different portions of the colon in one patient. In all of the samples, BRAF-V600E was the only common somatic mutation detected. In the patient from whom the three SSP samples were taken, the mutation was found in each polyp, but not in grossly uninvolved colon from the same patient.

The investigators next performed genomewide DNA methylation profiling on 15 colon biopsy samples from 11 patients, including five SSPs, two traditional serrated adenomas, three FAPs, two carcinomas, one grossly uninvolved tissue sample, and two normal tissue samples. They found that the BRAF-V600E mutation correlated with a unique and reproducible DNA methylation signature.

They then determined that the DNA methylation signature that they identified is associated with specific markers for molecular characterization of SSPs, and that these markers showed an approximately 3- to 30-fold increase in methylation levels in only SSP samples.

Furthermore, they showed that the unique DNA methylation patterns they identified could be used to distinguish SPPs from adenomatous polyps, with better discrimination than parallel-gene expression profiling.

"The results presented here provide strong evidence that the BRAF-V600E mutation is the main cause of generation of SSP and SSP-specific DNA methylation pattern," the investigators wrote in the study's conclusion.

The study was supported by grants from the National Institutes of Health and the Howard Hughes Medical Institute. The authors declared no competing financial interests in the work.

ginews@gastro.org

SOURCE: Jones D et al. PLOS One 13(3): e0192499.

Add antibiotics to resection

Gastric cancers *from page 1*

study. The results were published in the New England Journal of Medicine.

"We speculate that persistent inflammation of gastric mucosa with *H. pylori* infection promotes carcinogenesis and also increases tumor growth or invasiveness," said Il Ju Choi, MD, PhD, of the Center for Gastric Cancer, National Cancer Center, Goyang, South Korea, and coauthors.

Patients with early gastric cancers not at risk for lymph node metastasis may benefit from endoscopic resection. However, these patients are at high risk of developing new gastric cancer, and usually experience glandular atrophy, or advanced loss of mucosal glandular tissue, the authors said.

One nonrandomized study suggested *H. pylori* eradication could prevent development of subsequent cancers after endoscopic resection, according to the authors, but subsequent open-label trials were inconsistent on whether the treatment reduced cancer incidence.

Accordingly, Dr. Choi and colleagues conducted a prospective, double-blind, placebo-controlled, randomized trial of 470 patients who underwent endoscopic resection for high-grade adenoma or early gastric cancer.

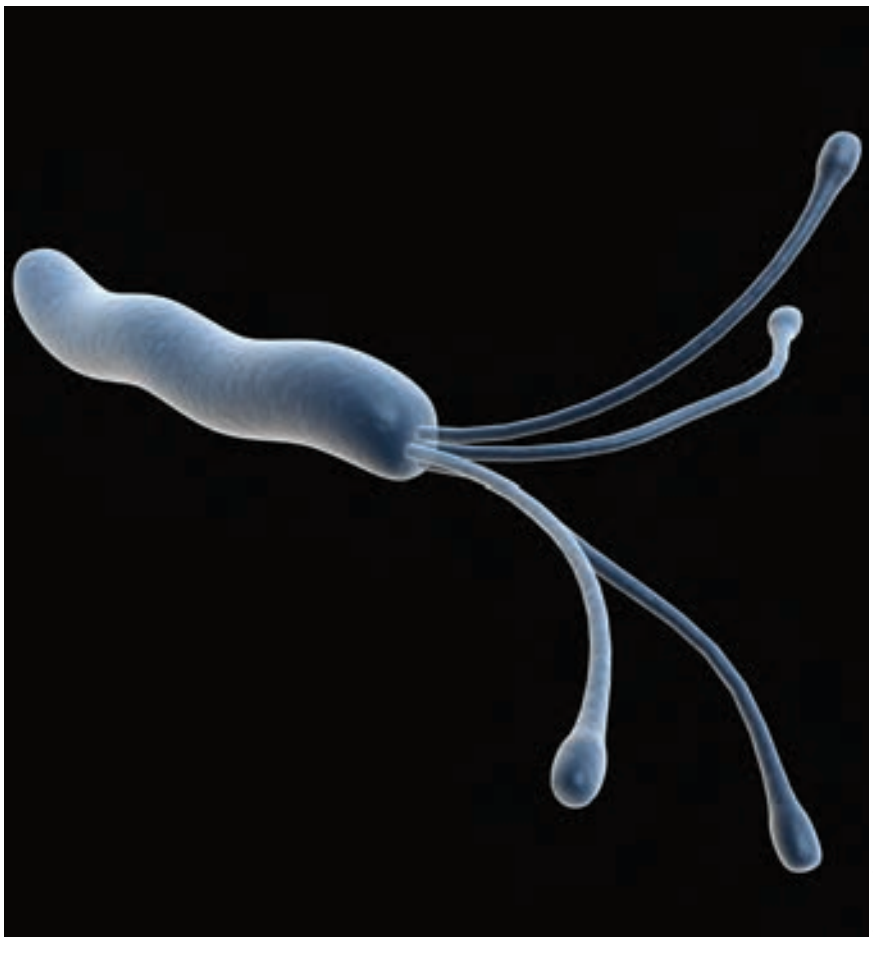
Of 396 patients included in an intention-to-treat analysis, 194 were randomized to receive antibiotics for *H. pylori* eradication, and 202 received placebo.

'We speculate that persistent inflammation of gastric mucosa with *H. pylori* infection promotes carcinogenesis and also increases tumor growth or invasiveness.'

Over a median follow-up of 5.9 years, new gastric cancers developed in 14 patients (7.2%) who received treatment, and in 27 patients (13.4%) who received placebo (hazard ratio, 0.50; 95% confidence interval, 0.26-0.94; $P = .03$).

Histologic analysis, performed in 327 patients, showed that 48.4% of patients in the treatment group showed improvement in atrophy grade at the gastric corpus lesser curvature, compared with just 15.0% of patients in the placebo group (*P*

Continued on page 18



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Continued from page 16

less than .001), the investigators reported.

Mild adverse events were more frequent in the treatment arm (42.0% versus 10.2%; *P* less than .001), and there were no serious adverse events, they added.

Despite the approximate 50% reduction in incidence of new gastric cancers and histologic improvements, the researchers said that further study would be required to optimize treatment approaches for patients undergoing endoscopic resection for high-grade adenoma or early gastric cancer.

"*H. pylori* eradication reduces, but cannot completely abolish, the risk of metachronous gastric cancer," wrote Dr. Choi and colleagues. "Thus, molecular markers, including aberrant methylation at specific genes, might help to identify high-risk patients even after successful eradication."

The researchers reported that they had nothing to disclose related to the study.

ginews@gastro.org

SOURCE: Choi IJ et al. N Engl J Med. 2018 Mar 22. doi: 10.1056/NEJMoa1708423.

PERSPECTIVE

Striking result in early gastric cancer

The study by Choi and colleagues suggests *Helicobacter pylori* eradication is effective at stopping the carcinogenic process in patients with severe chronic atrophic gastritis, an advanced precursor lesion to gastric cancer, according to Peter Malfertheiner, MD.

"It is a striking finding that *H. pylori* eradication may still be effective at this stage, since such therapy decreased the development of gastric cancer by 50% in this trial," Dr. Malfertheiner wrote in an editorial.

In the randomized, placebo-controlled trial, *H. pylori* eradication after endoscopic removal of early-stage disease effectively prevented metachronous gastric cancers (i.e., those detected on endoscopy at 1-year follow-up or thereafter) with a hazard ratio of 0.50, Dr. Malfertheiner noted.

The results confirm and strengthen previous findings by showing a significant improvement in atrophic gastritis, he added.

"In this endoscopic procedure, removal of early gastric cancer or high-grade adenoma leaves the stomach largely conserved but with the atrophic gastric mucosa remaining in a preneoplastic 'alarm state,' " he noted.

However, the potential link between cancer recurrence and atrophic gastritis was not explored in this particular study report, Dr. Malfertheiner said. Thus, it is unclear whether gastric cancer recurrence was prevented specifically in the subset of patients with atrophic gastritis.

It could be that eradication of *H. pylori* directly arrests carcinogenic mechanisms directly by ending persistent inflammation, he speculated.

"The beneficial effect may also be mediated by an alteration in the composition of the gastric microbiota because of improvement in the grade of gastric atrophy and a return toward normal gastric acid production," he added.

Dr. Malfertheiner is with the Clinic of Gastroenterology, Otto von Guericke University, Magdeburg, Germany. These comments are derived from his editorial (N Engl J Med. 2018 Mar 22. doi: 10.1056/NEJMe1800147). Dr. Malfertheiner reported personal fees from Allergan, Biohit, and Infai outside the submitted editorial.

Obesity in adults continues to rise

BY RICHARD FRANKI
MDedge News

Obesity and severe obesity rose significantly in adults but not in children from 2007 to 2016, according to data from the National Health and Nutrition Examination Survey.

The age-standardized prevalence of obesity – defined as a body mass index of 30 or more – among adults aged 20 years and over increased from 33.7% for the 2-year period of 2007-2008 to 39.6% in 2015-2016, while the prevalence of severe obesity – defined as a body mass index of 40 kg/m^2 or more – went from 5.7% to 7.7% over that same period, Craig M. Hales, MD, and his associates at the Centers for Disease Control and Prevention in Hyattsville, Md., and Atlanta said in a research letter published in JAMA.

The prevalence of obesity in children aged 2-19 years – defined as BMI at or above the sex-specific 95th percentile – increased, but not significantly, from 16.8% in 2007-2008 to 18.5% in 2015-2016, with most of that increase coming in the last 2 years. Severe obesity – BMI at or above 120% of the sex-specific 95th percentile – rose from 4.9% to 5.6% over those 10 years, but the last 2-year period saw the rate drop from 6% in 2013-2014, the investigators reported.

For the most recent reporting period, boys were more likely than girls to be obese (19.1% vs. 17.8%) and severely obese (6.3% vs. 4.9%), and both obesity and severe obesity were more common with increasing age.

Obesity prevalence went from 13.9% in those aged 2-5 years to 20.6% in 12- to 19-year-olds, and severe obesity was 1.8% in the youngest group and 7.7% in the oldest, with the middle-age group (6-11 years) in the middle in both categories, they said.

Among the adults, obesity was more common in women than men (41.1% vs. 37.9%) for 2015-2016, as was severe obesity (9.7% vs. 5.6%). Obesity and severe obesity were both highest in those aged 40-59 years, but obesity prevalence was lowest in the younger group (20-39 years) and severe obesity was least common in the older group (60 years and older), Dr. Hales and his associates said.

The analysis involved 16,875 children and 27,449 adults over the 10-year period. The investigators did not report any conflicts of interest.

rfranki@mdedge.com

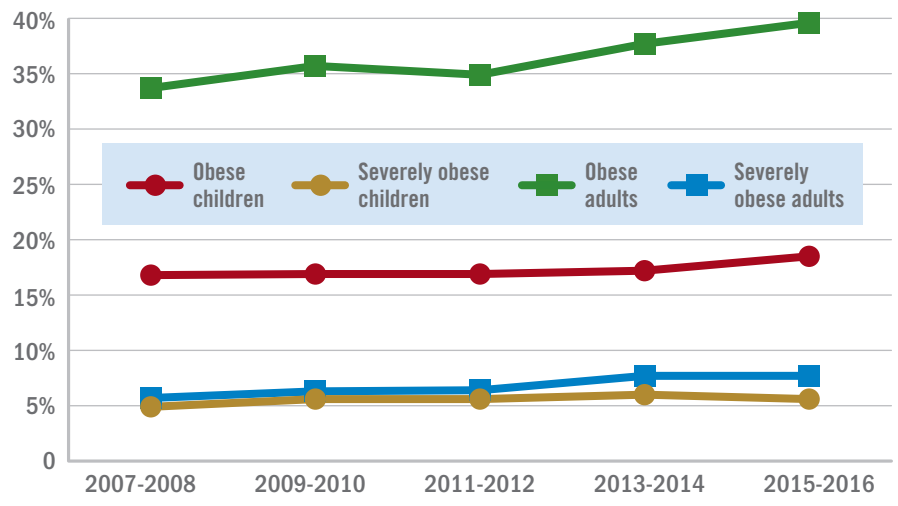
SOURCE: Hales CM et al. JAMA. 2018 Mar 23. doi: 10.1001/jama.2018.3060.

AGA Resource

AGA patient education materials can help your patients better understand how to manage and discuss obesity, including lifestyle, pharmacological, and endoscopic treatment options. Learn more at

www.gastro.org/patientInfo/topic/obesity.

Obesity prevalence trends in children and adults



Note: Based on data for 16,875 children aged 2-19 years and 27,449 adults from the National Health and Nutrition Examination Survey.

Source: JAMA. 2018 Mar 23. doi: 10.1001/jama.2018.3060

It is an exciting time in obesity treatment

BY LORA T. MCGLADE
MDedge News

BOSTON – For those in obesity treatment, things are looking up, said Reem Z. Sharaiha, MD, MSc, in a video interview at the AGA Tech Summit, sponsored by the AGA Center for GI Innovation and Technology. There are several new therapies to choose from, said Dr. Sharaiha, assistant professor of medicine at Cornell University, New York – and a variety of therapies coming down the pipeline. The key is to choose the right treatment, or right combination of treatments – surgical, endoscopic, or medical – for the right patient at the right time and to follow up.

In a panel discussion at the meeting on this topic, bariatric surgeon Mariana Kurian, MD, a clinical associate professor at NYU Langone Medical Center, New York, noted that even the procedures that produce the greatest restriction of food absorption are not typically effective as a single therapeutic approach. Her major point was that no approach, whether surgical, endoscopic, or lifestyle is generally sufficient to achieve and maintain weight loss indefinitely.

"Those of us working in obesity are very aware of its chronicity and how one intervention is not enough, Dr. Kurian said. She suggested that coordinated care among surgeons, gastroenterologists, dieticians, behavioral therapists, and others will provide the road forward even if the next set of surgical procedures or endoscopic devices are incrementally more effective than current options for weight loss.

One reason that a single intervention may not be enough is that obesity is not a single disease but the product of multiple pathological processes, according to Lee Kaplan, MD, PhD, AGAF, director of the Massachusetts General Hospital Weight Center, Harvard Medical School, Boston, who was also serving on the panel. He noted that, although there are large weight reductions with the most successful therapies, some patients are exceptional responders, while a proportion of patients lose little or no weight.

Dr. Reem Z. Sharaiha discussed developments in management of obesity at the AGA Tech Summit. Watch the video at https://www.mdedge.com/gihepnews.

Obesity is a chronic disease that needs long-term, team treatment. With obesity treatments there is sometimes a trade-off between risk and results, but the innovations coming along may balance that risk-results equation for some patients, Dr. Shariaha said.

lmcglade@mdedge.com

In Focus
Brought To You By The New Gastroenterologist

Underserved populations and colorectal cancer screening: Patient perceptions of barriers to care and effective interventions

BY IBIRONKE ODUYEBO, MD; MIGUEL MALESPIN, MD; ANTONIO MENDOZA LADD, MD; LUKEJOHN W. DAY, MD, AGAF; ALINE CHARABATY, MD; CHIEN-HUAN CHEN, MD, PHD, AGAF; ROTONYA M. CARR, MD; SANDRA QUEZADA, MD, MS; AND ESI LAMOUSÉ-SMITH, MD, PHD

Dr. Oduyebo is a third-year fellow at the Mayo Clinic, Rochester, Minn.; **Dr. Malespin** is an assistant professor in the department of medicine and the medical director of hepatology at the University of Florida Health, Jacksonville; **Dr. Mendoza Ladd** is an assistant professor of medicine at Texas Tech University, El Paso; **Dr. Day** is an associate professor of medicine at the University of California, San Francisco; **Dr. Charabaty** is an associate professor of medicine and the director of the IBD Center in the division of gastroenterology at Medstar-Georgetown University Center, Washington; **Dr. Chen** is an associate professor of medicine, the director of patient safety and quality, and the director of the small-bowel endoscopy program in division of gastroenterology at Washington University, St. Louis; **Dr. Carr** is an assistant professor of medicine in the division of gastroenterology at the University of Pennsylvania, Philadelphia; **Dr. Quezada** is an assistant dean for admissions, an assistant dean for academic and multicultural affairs, and an assistant professor of medicine in the division of gastroenterology and hepatology at the University of Maryland, Baltimore; and **Dr. Lamousé-Smith** is a director of translational medicine, immunology, and early development at Janssen Pharmaceuticals Research and Development, Spring House, Pa.

Despite the positive public health effects of colorectal cancer (CRC) screening, there remains differential uptake of CRC screening in the United States. Minority populations born in the United States and immigrant populations are among those with the lowest rates of CRC screening, and both socioeconomic status and ethnicity are strongly associated with stage of CRC at diagnosis.[1,2] Thus, recognizing the economic, social, and cultural factors that result in low rates of CRC screening in underserved populations is important in order to devise targeted interventions to increase CRC uptake and reduce morbidity and mortality in these populations.

What are the facts and figures?

The overall rate of screening colonoscopies has increased in all ethnic groups in the past 10 years but still falls below the goal of 71% established by the Healthy People project (www.healthypeople.gov) for the year 2020.[3] According to the Centers for Disease Control and Prevention ethnicity-specific data for U.S.-born populations, 60% of whites, 55% of African Americans (AA), 50% of American Indian/Alaskan natives (AI/AN), 46% of Latino Americans, and 47% of Asians undergo CRC screening (Figure 1A).[4] While CRC incidence in non-Hispanic whites age 50 years and older has dropped by 32% since 2000 because of screening, this trend has not been observed in AAs.[5,6]

The incidence of CRC in AAs is estimated at 49/10,000, one of the highest amongst U.S. populations and is the second and third most common cancer in AA women and men, respectively (Figure 1B).

Similar to AAs, AI/AN patients present with more advanced CRC disease and at younger ages and have lower survival rates, compared with other racial groups, a trend that has not changed in the last decade.[7] CRC screening data in this population vary according to sex, geographic location, and health care utilization, with as few as 4.0% of asymptomatic, average-risk AI/ANs who receive medical care in the Indian Health Services being screened for CRC.[8]

The low rate of CRC screening among Latinos also poses a significant obstacle to the Healthy People project since it is expected that by 2060 Latinos will constitute 30% of the U.S. population. Therefore, strategies to improve CRC screening in this population are needed to continue the gains made in overall CRC mortality rates.

The percentage of immigrants in the U.S. population increased from 4.7% in 1970 to 13.5% in 2015. Immigrants, regardless of their ethnicity, represent a very vulnerable population, and CRC screening data in this population are not as robust as for U.S.-born groups. In general, immigrants have substantially lower CRC screening rates, compared with U.S.-born populations (21% vs. 60%),[9] and it is suspected that additional, significant barriers to CRC screening and care exist for undocumented immigrants.

Another often overlooked group, are individuals with physical or cognitive disabilities. In this group, screening rates range from 49% to 65%.[10]

Finally, while information is available for many health care conditions and disparities faced by various ethnic groups, there are few CRC screening data for the LGBTQ community. Perhaps amplifying this problem is the existence of conflicting data in this population, with some studies suggesting there is no difference in CRC risk across groups in the LGBTQ community and others suggesting an increased risk.[11,12] Notably, sexual orientation has been identified as a positive predictor of CRC screening in gay and bisexual men – CRC screening rates are higher in these groups, compared with heterosexual men.[13] In contrast, no such difference has been found between homosexual and heterosexual women.[14]

As we all strive to improve the rate of colorectal cancer screening, it is important to acknowledge that barriers exist that prevent screening uptake. Importantly, these barriers often vary between specific population subsets. In this month's In Focus article, brought to you by *The New Gastroenterologist*, the members of the AGA Institute Diversity Committee provide an enlightening overview of the barriers affecting underserved populations as well as strategies that can be employed to overcome these impediments. Better understanding of patient-specific barriers will, I hope, allow us to more effectively redress them and ultimately increase colorectal cancer screening rates in all populations.

Bryson W. Katona, MD, PhD
Editor in Chief, The New Gastroenterologist

What are the barriers?

Several common themes contribute to disparities in CRC screening among minority groups, including psychosocial/cultural, socioeconomic, provider-specific, and insurance-related factors. Some patient-related barriers include issues of illiteracy, having poor health literacy or English proficiency, having only grade school education,[15,16] cultural misconceptions, transportation issues, difficulties affording copayments or deductibles, and a lack of follow-up for scheduled appointments and exams.[17-20] Poor health literacy has a profound effect on exam perceptions, fear of test results, and compliance with scheduling tests and bowel preparation instructions[21-25]; it also affects one's understanding of the importance of CRC screening, the recommended screening age, and the available choice of screening tests.

Even when some apparent barriers are mitigated, disparities in CRC screening remain. For example, even among the insured and among Medicare beneficiaries, screening rates and adequate follow-up rates after abnormal findings remain lower among AAs and those of low socioeconomic status than they are among whites.[26-28] At least part of this paradox results from the presence of unmeasured cultural/belief systems that affect CRC screening uptake. Some of these factors include fear and/or denial of CRC diagnoses, mistrust of the health care system, and reluctance to undergo medical treatment and surgery.[16,29] AAs are also less likely to be aware of a family history of CRC and to discuss personal and/or family history of CRC or polyps, which can thereby hinder the identification of high-risk individuals who would benefit from early screening.[15,30]

The deeply rooted sense of fatalism also plays a crucial role and has been cited for many minority and immigrant populations. Fatalism leads patients to view a diagnosis of cancer as a matter of "fate" or "God's will," and therefore, it is to be endured.[23,31] Similarly, in a qualitative study of 44 Somali men living in St. Paul and Minneapolis, believing cancer was more common in whites, believing they were protected from cancer by God, fearing a cancer diagnosis, and fearing ostracism from their community were reported as barriers to cancer screening.[32]

Perceptions about CRC screening methods in Latino populations also have a tremendous influence and can include fear, stigma of sexual prejudice, embarrassment of being exposed during the exam, worries about humiliation in a male sense of masculinity, a lack of trust in the medical professionals, a sense of being a "guinea pig" for physicians, concerns about health care racism, and expectations of pain.[33-37] Studies have reported that immigrants are afraid to seek health care because of the increasingly hostile environment associated with immigration enforcement.[38] In addition, the impending dissolution of the Deferred Action for Childhood Arrivals act is likely to augment the barriers to care for Latino groups.[39]

In response to the alarming disparity in CRC screening rates in Latino communities, several interventions have been set in motion in different clinical scenarios, which include patient navigation and a focus on patient education.

In addition, provider-specific barriers to care also exist. Racial and ethnic minorities are less likely than whites to receive recommendations for screening by their physician. In fact, this factor alone has been demonstrated to be the main reason for lack of screening among AAs in a Californian cohort.[40] In addition, patients from rural areas or those from AI/AN communities are at especially increased risk for lack of access to care because of a scarcity of providers along with patient perceptions regarding their primary care provider's ability to connect them to subspecialists.[41-43] Other cited examples include misconceptions about and poor treatment of the LGBTQ population by health care providers/systems.[44]

How can we intervene successfully?

Characterization of barriers is important because it promotes the development of targeted interventions. Intervention models include community engagement programs, incorporation of fecal occult testing, and patient navigator programs.[45-47] In response to the alarming disparity in CRC screening rates in Latino communities, several interventions have been set in motion in different clinical scenarios, which include patient navigation and a focus on patient education.

Patient navigators facilitate the screening process at different stages, including providing information that is easy to understand by pa-

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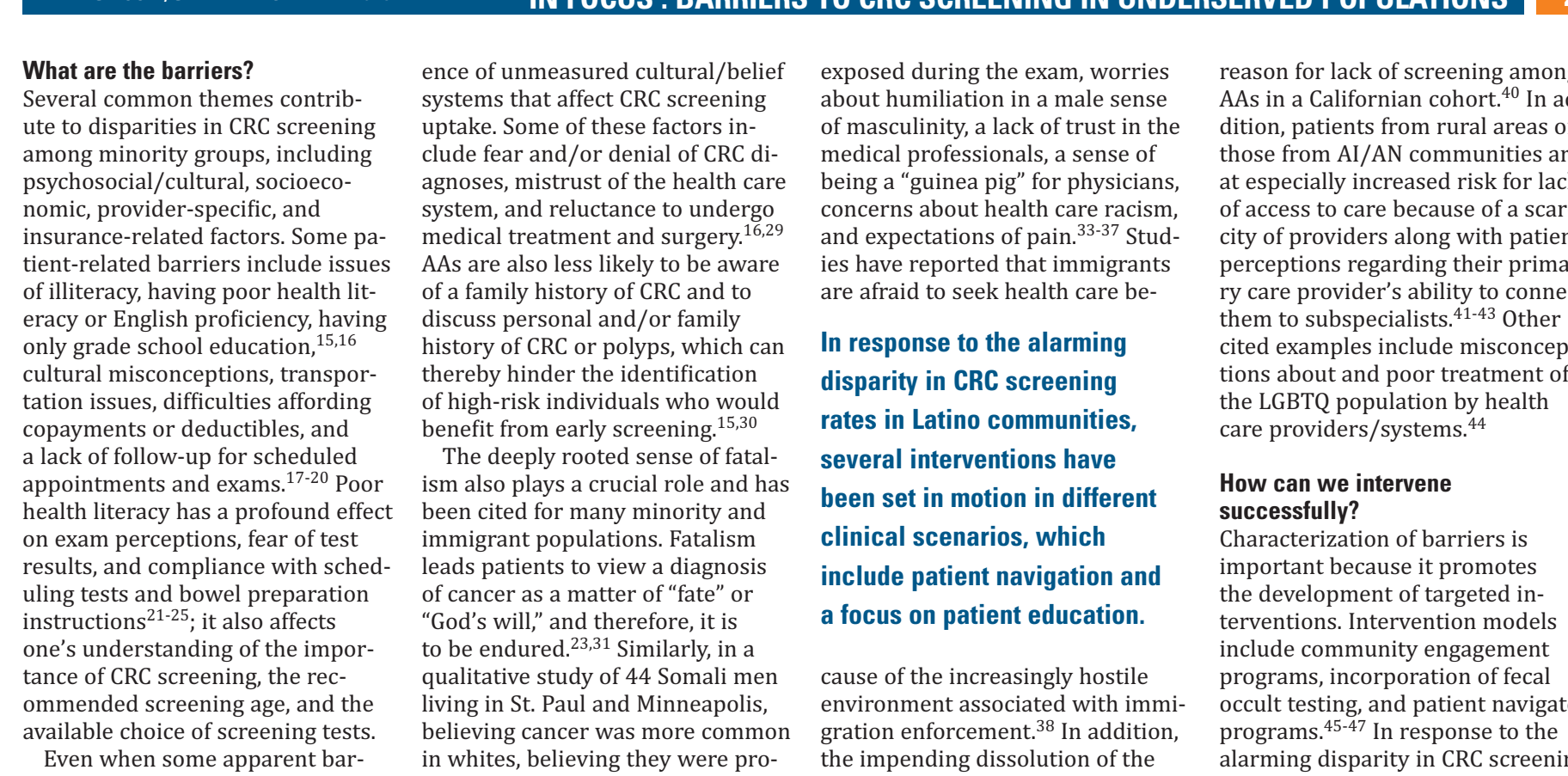

Figure 1. A) Self-described colorectal screening rates for ethnic minority groups (A/PI, Asian Pacific Islander; AI/AN, American Indian/Alaskan Native) are consistent with Centers for Disease Control ethnicity-specific data for US-born populations rates of CRC screening: 60% of Whites, 55% of African Americans, 50% of American Indian/Alaskan natives (AI/AN), 46% of Latino Americans and 47% of Asians. This article was published in American Journal of Preventive Medicine, 46, David T. Liss and David W. Baker, Understanding Current Racial/Ethnic Disparities in Colorectal Cancer Screening in the United States, 228-36, Copyright Elsevier/American College of Preventive Medicine/Association for Prevention Teaching and Research (2014). B) colorectal cancer rates are highest among African Americans (Af. Am). This figure was published in Colorectal Cancer Rates by Race and Ethnicity (https://www.cdc.gov/cancer/colorectal/statistics/race.htm).

Continued from previous page

tients, translating when patients are not proficient in English, addressing any concerns they may have about the procedure, and reminding patients about their appointments via phone calls or other means (Figure 2). Trials evaluating the effect of patient navigators in Hispanic populations have resulted in anywhere from a modest 11% to a robust 56% increase in screening.[48-50] In facilities serving a large number of Latino patients with low socioeconomic status, low-cost interventions, such as mailing information about CRC screening to all eligible patients, increased the screening rate from 12% to 28%.[51] It has been shown that using bilingual and bicultural staff, language-appropriate material, and face-to-face encounters in a community setting helped recruit Chinese Americans into CRC screening trials.[52] Similarly, an activation educational program consisting of a video and brochure that actively encouraged patients to ask their primary care physicians about CRC screening resulted in a 10% increase in screening rates.[53]

Randomized trials have shown that outreach efforts and patient navigation increase CRC screening rates in AAs.[48,54,55] Studies evaluating the effects of print-based educational materials on improving screening showed improvement in screening rates, decreases in cancer-related fatalistic attitudes, and patients had a better understanding of the benefits of screening as compared with the cost associated with screening and the cost of advanced disease.[56] Similarly, the use of touch-screen computers that tailor informational messages to decisional stage and screening barriers increased participation in CRC screening.[57] Including patient navigators along with printed education material was even more effective at increasing the proportion of patients getting colonoscopy screening than providing printed material alone, with more-intensive navigation needed for individuals with low literacy.[58] Grubbs et al. reported the success of their patient navigation program, which included wider comprehensive screening and coverage for colonoscopy screening.[59] In AAs, they estimated an annual reduction of CRC incidence and mortality of 4,200 and 2,700 patients, respectively.

Courtesy AGA Institute

Figure 2. Patient Navigator programs are demonstrating effectiveness for improving colorectal screening rates in underserved and economically disadvantaged populations.

Among immigrants, there is an increased likelihood of CRC screening in those immigrants with a higher number of primary care visits.[60] The intersection of culture, race, socioeconomic status, housing enclaves, limited English proficiency, low health literacy, and immigration policy all play a role in immigrant health and access to health care.[61] Therefore, different strategies may be needed for each immigrant group to improve CRC screening. For this group of patients, efforts aimed at mitigating the adverse effects of national immigration policies on immigrant populations may have the additional consequence of improving health care access and CRC screening for these patients.

Data gaps still exist in our understanding of patient perceptions, perspectives, and barriers that present opportunities for further study to develop long-lasting interventions that will improve health care of underserved populations. By raising awareness of the barriers, physicians can enhance their own self-awareness to keenly be attuned to these challenges as patients cross their clinic threshold for medical care.

Additional resources link: www.cdc.gov/cancer/colorectal/

See references at gihepnews.com

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 14: Intraluminal gallbladder arterial hemorrhage as a complication of arteriosclerosis and anticoagulant therapy

This radiologic sign on multiphasic contrast-enhanced multidetector computed tomography with axial images (Figure A–C), coronal multiplanar reconstruction (Figure D), and coronal volume rendering technique were indicative for active hemorrhage of gallbladder wall. During the urgent surgical treatment, there was confirmation of that distended gallbladder. Postoperatively, opening of the gallbladder revealed in its lumen the presence of bile mixed with dishomogeneous blood clots. Pathologic evaluation demonstrated arteriosclerosis of the cystic artery, with a pseudoaneurysmatic tear of one of its collateral branches with focal surround inflammatory tissue of gallbladder wall. The postoperative course was uneventful, and the patient was discharged on day 8.

Hemorrhage from the gallbladder is not a frequent event.[1] The etiologies for hemorrhage of the gallbladder are trauma, neoplasms, inflammation of the wall with gallstones, aneurysms, varicose veins with portal hypertension, arteriosclerosis, and coagulopathy. However, isolated gallbladder arterial hemorrhage owing to anticoagulation therapy has been reported rarely. This pathologic state can be detected by contrast-enhanced ultrasound, contrast-enhanced computed tomography, and digital subtraction angiography.[2,3]

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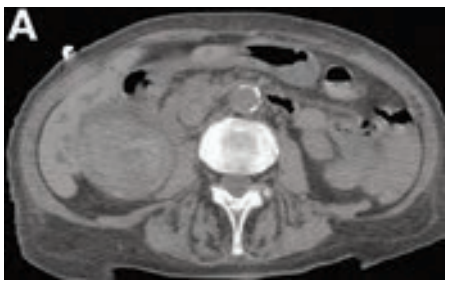

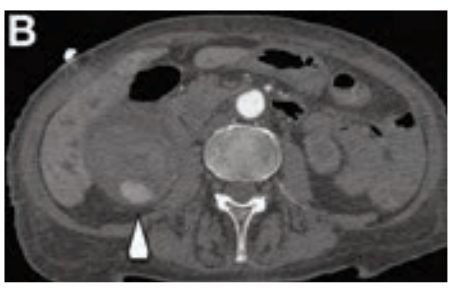

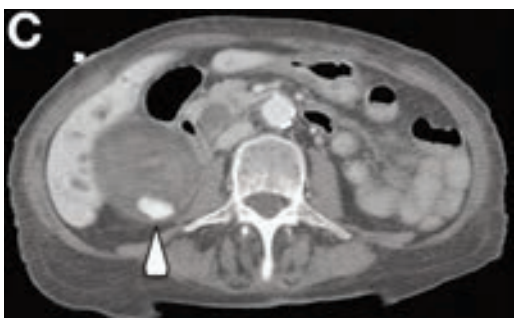

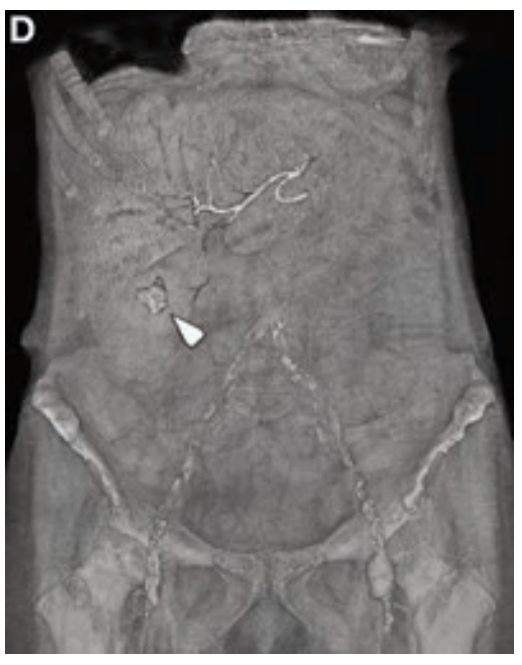

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GI & HEPATOLOGY NEWS

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Medical treatment of perianal fistulae often warranted

BY ANDREW D. BOWSER
MDedge News

PHILADELPHIA – Perianal fistulae are a common and difficult-to-treat complication of Crohn's disease that may often require medical therapy, though not all treatment options have robust data supporting their use in this setting, according to Mark T. Osterman, MD.

"Most studies done on fistulae actually didn't have that as the primary endpoint – it was a secondary endpoint, so they weren't really designed to look at fistulae, specifically," said Dr. Osterman, associate professor of medicine in the division of gastroenterology at the University of Pennsylvania in Philadelphia.

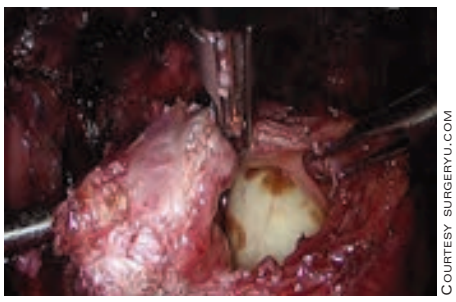
Dr. Osterman shared his own approach to medical treatment of perianal fistulae in a presentation he gave at Digestive Diseases: New Advances, jointly provided by Rutgers and Global Academy for Medical Education.

For simple perianal fistula with no rectal inflammation, a fistulotomy is reasonable, but medical treatment may be preferable, Dr. Osterman said.

"I always favor medical therapy because it attacks the root of the problem, which is the immune system," he explained.

Helpful treatments in this scenario include antibiotics, along with anti–tumor necrosis factor therapy with or without immunomodulators, he said.

Antibiotic use in this setting is based on uncontrolled data, and efficacy is modest at best, according to Dr. Osterman, who noted that the treatments may reduce fistula drainage but likely do not heal fistulae.



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A nodule is partially enucleated with an advanced bipolar device using a "squeeze" technique. A rectal probe, in the lumen of the rectum, will be used as a template for repair.

The most commonly used antibiotics are metronidazole and ciprofloxacin given for 2-4 months, he added.

Infliximab is the drug that has by far the most robust fistula data, and one of only two drugs where a fistula was the primary outcome of the studies, according to Dr. Osterman.

In a randomized trial, infliximab induction treatment more than doubled fistula-related response and remission rates, compared with placebo, he said.

Maintenance infliximab treatment likewise showed an approximate doubling of both response and remission of fistula versus placebo, he added.

While not designed to look at fistulae as a primary outcome, the randomized CHARM study of adalimumab versus placebo for maintenance of Crohn's disease remission did demonstrate remission rates about twice as high with the use of adalimumab, compared with placebo, in 117 patients who had draining fistulae at baseline, Dr. Osterman recounted.

For patients with complex fistulae, as well as patients with rectal inflammation, a seton and aggressive medical therapy are likely needed, Dr. Osterman said in his presentation.

An advancement flap or medical therapies such as vedolizumab or tacrolimus might be warranted for patients who fail other medical approaches, he added.

Relevant vedolizumab data come from GEMINI 2, a large clinical trial for Crohn's disease that included 57 patients who had draining fistulas at baseline.

"We see an improvement in remission rates with fistula with vedolizumab, compared to placebo, but again, [GEMINI 2] wasn't designed to look at fistula, but we do use it," said Dr. Osterman.

Tacrolimus is the only drug besides infliximab that has randomized data for fistula, according to Dr. Osterman.

In the small randomized study, 48 patients with Crohn's disease and draining perianal or enterocutaneous fistulae were treated for 10 weeks with oral tacrolimus at 0.2 mg/kg per day or placebo.

Fistula improvement was seen in 43% of tacrolimus-treated patients and 8% of placebo-treated patients ($P = .004$), while remission was seen in 10% and 8% of those groups, respectively ($P = .86$), according to published data on the trial.

"[Tacrolimus] showed a nice improvement in response rates, but very similar remission rates," Dr. Osterman said, "but it does represent an option for us, for our patients."

Dr. Osterman reported grant/research support from UCB and serving as a consultant for AbbVie, Janssen, Lycera, Merck, Pfizer, Takeda, and UCB.

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DPP-4 inhibitors increase IBD risk in diabetes

BY BIANCA NOGRADY
MDedge News

Dipeptidyl peptidase-4 inhibitors are associated with a 75% increase in the risk of inflammatory bowel disease (IBD) in individuals with type 2 diabetes, a study has found.

Researchers reported the results of an observational cohort study of 141,170 patients with type 2 diabetes newly treated with noninsulin antidiabetic drugs, with 552,413 person years of follow-up. Of these, 30,488 patients (21.6%) received at least one prescription for a dipeptidyl peptidase-4 inhibitor, and median duration of use was 1.6 years.

The report was published March 21 in the BMJ.

The researchers found that dipeptidyl peptidase-4 (DPP-4) inhibitors were associated with a 75% increased risk of IBD, compared with other antidiabetic drugs (53.4 vs. 34.5 per 100,000 per year; 95% confidence interval, 1.22-2.49).

The risk increased with longer duration of use, peaking at a nearly threefold increase in the risk of IBD after 3-4 years of taking DPP-4 inhibitors (hazard ratio 2.9; 95% CI, 1.31-6.41), and declining to a 45% increase in risk with 4 years of use.

"Although the absolute risk is low, physicians should be aware of this possible association and perhaps refrain from prescribing dipeptidyl peptidase-4 inhibitors for people at high risk (that is, those with a family history of disease or with known autoimmune conditions)," wrote Devin Abrahami of McGill University, Montreal, and coauthors. "Moreover, patients presenting with persistent gastrointestinal symptoms such as abdominal pain or diarrhoea should be closely monitored for worsening of symptoms."

The same pattern was seen with years since initiation of medication, with a peak in the risk of IBD seen at 3-4 years after initiation followed by a decline.

"This gradual increase in the risk is consistent with the hypothesis of a possible delayed effect of the use of dipeptidyl peptidase-4 inhibitors on the incidence of inflammatory bowel disease," the authors wrote.

When compared directly with insulin, the use of DPP-4 inhibitors was associated with an over twofold increase in the risk of IBD (HR, 2.28; 95% CI, 1.07-4.85).

The use of DPP-4 inhibitors was also associated with a greater than twofold increase in the risk of ulcerative colitis but no significant effect was seen for Crohn's disease. However, the authors noted that this result was based on relatively few events and should be interpreted with caution.

The research did not find any difference in risk across different DPP-4 inhibitor drugs.

The DPP-4 enzyme is known to be expressed on the surface of cell types involved in immune response, and patients with IBD have been found to have lower serum DPP-4 enzyme concentrations than healthy controls.

Yet the authors said this was the first study to their knowledge that specifically investigated the effect of DPP-4 inhibitor use on the incidence of IBD.

One previous observational study actually found a decreased risk of a composite outcome of several autoimmune disorders – including IBD – with the use of DPP-4 inhibitors, but it did not report on IBD specifically. The authors also noted that DPP-4 may have a different biological function in IBD.

The Canadian Institutes of Health Research funded the study. No conflicts of interest were declared.

ginews@gastro.org

SOURCE: Abrahami D et al. BMJ. 2018;360:k872.

Screening for Barrett's esophagus: Consider risk

BY IAN LACY
MDedge News

Screening and surveillance practices for Barrett's esophagus are varied, but there are a variety of approaches researchers have taken to find the best strategy.

The evidence discussed in this article supports the current recommendation of GI societies that screening endoscopy for Barrett's esophagus be performed only in well-defined, high-risk populations. Alternative tests for screening are not now recommended; however, some of the alternative tests show great promise, and it is expected that they will soon find a useful place in clinical practice. At the same time, there should be a complementary focus on using demographic and clinical factors as well as noninvasive tools to further define populations for screening. All tests and tools should be balanced with the cost and potential risks of the screening proposed.

Stuart Spechler, MD, AGAF, of the University of Texas and his colleagues looked at a variety of techniques, both conventional and novel, as well as the cost-effectiveness of these strategies in a commentary published in the May issue of Gastroenterology.

Some studies have shown that endoscopic surveillance programs have identified early-stage cancer and provided better outcomes, compared with patients presenting after they already have cancer symptoms. One meta-analysis included 51 studies with 11,028 subjects and demonstrated that patients who had surveillance-detected esophageal adenocarcinoma (EAC) had a 61% reduction in their mortality risk. Other studies have shown similar results, but are susceptible to certain biases. Still other studies have refuted that the surveillance programs help at all. In fact, those with Barrett's esophagus who died of EAC underwent similar surveillance compared with controls in those studies, showing that surveillance did very little to improve their outcomes.

One strategy has been to identify patients with Barrett's esophagus and develop a tool based on demographic and historical information. Tools like this have shown lukewarm results, with areas under the receiver operating characteristic curve (AUROC) ranging from 0.61 to 0.75. One study used information concerning obesity, smoking history, and increasing age, combined with weekly symptoms of gastroesophageal reflux and found that this improved results by nearly 25%. Modified versions of this model have also shown improved detection. When Thrift et al. added additional factors like education level, body mass index, smoking status, and more serious alarm symptoms like unexplained weight loss, the model was able to improve AUROC scores to 0.85 (95% confidence interval, 0.78-0.91). The clinical utility of these models is still unclear. Nonetheless, these models have influenced certain GI societies that believe in endoscopic screening only of patients with additional risk factors.

Alternative tests for screening are not now recommended; however, some of the alternative tests show great promise, and it is expected that they will soon find a useful place in clinical practice.

Although predictive models may assist in identifying at-risk patients, endoscopes are still needed to diagnose. Transnasal endoscopes (TNEs), tend to be better tolerated by patients and result in less gagging. One study showed that TNEs (45.7%) improved participation, compared with standard endoscopy (40.7%). Despite the positives, TNEs provided significantly lower biopsy acquisitions than standard endoscopes (83% vs. 100%, $P = .001$) because of the sheathing on the endoscope. Other studies have demonstrated the strengths of TNEs, including a study in which 38% of patients had a finding that changed management of their disease. TNEs should be considered a reliable screening tool for Barrett's esophagus.

Other advances in imaging technology like the advent of the high-resolution complementary metal oxide semiconductor (CMOS), which is small enough to fit into a pill capsule, have led researchers to look into its effectiveness as a screening tool for Barrett's esophagus. One meta-analysis of 618 patients found that the pooled sensitivity and specificity

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for diagnosis were 77% and 86%, respectively. Despite its ability to produce high-quality images, the device remains difficult to control and lacks the ability to obtain biopsy samples.

Another example of a swallowed medical device, the Cytosponge-TFF3 is an ingestible capsule that degrades in stomach acid. After 5 minutes, the capsule dissolves and releases a mesh sponge that will be withdrawn through the mouth, scraping the esophagus and gathering a sample. The Cytosponge has proven effective in the Barrett's Esophagus Screening Trials (BEST) 1. BEST 2 looked at 463 controls and 647 patients with Barrett's esophagus across 11 U.K. hospitals. The trial showed that the Cytosponge exhibited sensitivity of 79.9%, which increased to 87.2% in patients with more than 3 cm of circumferential Barrett's metaplasia.

Breaking from the invasive nature of imaging scopes and the Cytosponge, some researchers are looking to use "liquid biopsy" to detect abnormalities in the blood like DNA or microRNA (miRNA) to identify precursors or presence of a disease. One study found that patients with Barrett's esophagus had increased levels of miRNA-194, -215, and -143 but these findings were not validated in a larger study. Other studies have demonstrated similar findings, but more research must be done to validate these findings in larger cohorts.

Other novel detection therapies have been investigated, including serum adipokine and electronic nose breathing tests. The serum adipokine test looks at the metabolically active adipokines secreted in obese patients and those with metabolic syndrome to see if they could predict the presence of Barrett's esophagus. Unfortunately, the data appear to be conflicting, but these tests can be used in conjunction with other tools to detect Barrett's esophagus. Electronic nose tests also work by detecting metabolically active compounds from human and gut bacterial metabolism. One study found that analyzing these volatile compounds could delineate between Barrett's and non-Barrett's patients with 82% sensitivity, 80% specificity, and 81% accuracy. Both of these technologies need large prospective studies in primary care to validate their clinical utility.

AGA Resource

AGA patient education on Barrett's esophagus will help your patients better understand the disease and how to manage it. Learn more at gastro.org/patient-care.

While the adoption of a new screening strategy could succeed where others have failed, Dr. Spechler points out the potential harm.

"There also is potential for harm in identifying asymptomatic patients with Barrett's esophagus. In addition to the high costs and small risks of standard endoscopy, the diagnosis of Barrett's esophagus can cause psychological stress, have a negative impact on quality of life, result in higher premiums for health and life insurance, and might identify innocuous lesions that lead to potentially hazardous invasive treatments. Efforts should therefore be continued to combine biomarkers for Barrett's with risk stratification. Overall, while these vexing uncertainties must temper enthusiasm for the unqualified endorsement of any screening test for Barrett's esophagus, the alternative of making no attempt to stem the rapidly rising incidence of a lethal malignancy also is unpalatable."

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ilacy@mdedge.com

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Survival worse with alcohol-related HCC

BY NEIL OSTERWEIL
MDedge News

Hepatocellular carcinoma (HCC) related to alcohol use tends to be diagnosed at a later stage than HCC from other causes, which contributes to reduced overall survival among patients with alcoholic HCC, investigators in a prospective French study said.

Among 894 patients diagnosed with HCC, the adjusted median overall survival was 5.7 months for those with alcoholic HCC, compared with 9.7 months for those with nonalcoholic HCC (*P* = .0002), reported Charlotte E. Costentin, MD, of the Hopital Henri Mondor in Creteil, France, and colleagues.

"Various assumptions can be made to explain why patients with alcohol-related HCC have reduced survival in comparison with patients with non–alcohol-related HCC: a diagnosis at a later stage due to lower rates of HCC screening, worse liver function and/or ongoing alcohol consumption preventing curative options, and discrimination against alcoholic patients leading to less aggressive treatment options," they wrote in a study published online in Cancer.

The investigators looked at data on clinical features and treatment allocation of patients in the CHANGH cohort (cohorte de Carcinomes Hepatocelulaires de l'Association des hepato-Gastroenterologues des Hopitaux Generaux), a prospective, observational cohort study.

Of 1,207 patients with complete data, 582 had isolated alcohol-related HCC, and 312 had non–alcohol-related HCC, which was caused by either nonalcoholic fatty liver, hepatitis C infections, hepatitis B infections, hemochromatosis, or other etiologies.

As noted before, the median overall survival adjusted for lead-time bias (the length of time between the detection of a disease and its usual diagnosis) was significantly shorter for patients with alcohol-related HCC.

In univariate analysis, alcohol-related HCC, compared with non–alcohol-related HCC, was an independent risk factor for worse overall survival (hazard ratio, 1.39; *P* = .0002).

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Among patients in the alcohol-related HCC group, median overall survival adjusted for lead-time was 5.8 months for patients who had been abstinent for a median of 1 year, compared with 5.0 months for the nonabstinent patients, a difference that was not statistically significant.

In multivariate analysis, factors significantly associated with worse overall survival included advanced HCC at diagnosis (diffuse or metastatic HCC and/or macrovascular invasion), alkaline phosphatase score, alpha-fetoprotein levels, creatinine, performance status, Child-Pugh score, age plus alcohol-related disease, and male sex plus alcohol-related disease. However, alcohol-related versus non–alcohol-related HCC was no longer statistically significant in multivariate analysis.

They noted that, for 199 patients who were diagnosed with HCC as part of a cirrhosis follow-up program, the median overall survival adjusted for lead-time was 11.7 months, compared with 5.4 months for patients whose HCC was detected incidentally (*P* less than .0001).

"Importantly, Bucci et al. (Aliment Pharmacol Ther. 2016 Feb;43[3]:385-99) observed similar survival between alcoholic patients and patients with hepatitis C virus among patients undergoing HCC surveillance according to guidelines. The poorer prognosis of alcohol-related HCC is, therefore, very likely to be related to an advanced stage at diagnosis due to screening failure instead of greater cancer aggressiveness," they wrote.

"To improve prognosis of liver cancer in the alcoholic population, efforts should be made to implement effective screening programs for both cirrhosis and liver cancer and to improve access to alcoholism treatment services," Dr. Costentin said in press release. "A smaller tumor burden and a better liver function at diagnosis should translate into higher rates of patients with alcohol-related liver cancer amenable to curative treatment such as tumor resection or ablation and liver transplantation."

Dr. Costentin reported no conflicts of interest. Several of her coauthors reported personal fees from companies outside the submitted work.

ginews@gastro.org

SOURCE: Costentin CE at al. Cancer. doi: 10.1002/cncr.31215.

SGLT-2 inhibitor reduced liver fat in NAFLD with diabetes

BY ELI ZIMMERMAN
MDedge News

CHICAGO – Empagliflozin, an oral sodium-glucose cotransporter 2 (SGLT-2), reduced liver fat by 5% and improved ALT in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus, according to a study presented at the annual meeting of the Endocrine Society.

As insulin resistance is the mechanism for NAFLD development, this new addition to the list of drugs for patients with diabetes could help decrease the chance of developing metabolic syndrome and cardiovascular disease.

"SGLT-2 inhibitors are newer antidiabetic agents that reduce blood glucose by promoting urinary glucose excretion," said presenter Mohammad Shafi Kuchay, MD, DM, an endocrinologist at Medanta The Medicity, Gurugram, India. "NAFLD, which also increases the risk of type 2 diabetes, often responds to strategies that improve hyperglycemia."

Dr. Kuchay and fellow investigators conducted a small, 20-week randomized controlled trial of 42 patients with type 2 diabetes and NAFLD.

Patients in the test group were mostly male and on average 50 years old, with baseline AST, ALT, and gamma-glutamyltransferase scores of 44.6 U/L, 64.3 U/L, and 65.8 U/L, respectively. Those randomized to the control group had similar characteristics.

After addition of 10 mg of empagliflozin to their diabetes regimen, liver fat density in test patients decreased from 16.2% to 11.3% (*P* less than or equal to .0001). The drop stands in sharp contrast to the control group, which decreased from 16.4% to 15.5% (*P* = .054). Measurement of liver fat density was made by MRI-derived proton density fat fraction (MRI-PDFF). This method has higher sensitivity for detecting changes in liver fat, compared with histology, explained Dr. Kuchay.

When broken down by individual liver fat, 25% of patients in the control group increased in liver fat, 50% had no significant change, and 25% decreased in liver fat, according to Dr. Kuchay. In comparison, 77% of patients in the empagliflozin group had a decrease in liver fat, 23% had no change, and none saw an increase in liver fat.

Both groups had a similarly significant reduction of around 2% of hemoglobin A_{1c}, which Dr. Kuchay attributes to deliberate intervention by investigators.

Further studies will need to be conducted regarding the long-term effects of this treatment; however, using SGLT-2 to reduce liver fat could be a boon to preventing more serious liver diseases, concluded Dr. Kuchay.

"There are studies in which liver fat reduction led to improvement in inflammation and fibrosis," said Dr. Kuchay in response to a question from the audience.

Dr. Kuchay had no disclosures.

ezimmerman@mdedge.com

SOURCE: Kuchay M et al. ENDO 2018, Abstract OR27-2.

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Switching to tenofovir alafenamide may help for HBV

BY ANDREW D. BOWSER
MDedge News

PHILADELPHIA – Tenofovir alafenamide, the newest kid on the block for treatment of chronic hepatitis B, not only has less bone and renal effects than tenofovir disoproxil, but now also appears to improve those parameters in patients switched over from the older tenofovir formulation, according to Paul Kwo, MD.

Dr. Kwo, director of hepatology at Stanford (Calif.) University, described some of the latest data on the newer tenofovir formulation in a hepatitis B update he gave at Digestive Diseases: New Advances, jointly provided by Rutgers and Global Academy for Medical Education.

Tenofovir alafenamide, a nucleoside analogue reverse transcriptase inhibitor, was approved in November 2016 for treatment of adults with chronic hepatitis B virus (HBV) infection and compensated liver disease.

It has similar efficacy to tenofovir disoproxil, with fewer bone and renal effects, according to results of two large international phase 3 trials.

Some of the latest data, presented in October 2017 at The Liver Meeting in Washington, show that switching patients from tenofovir disoproxil to tenofovir alafenamide improved creatinine clearance and increased rates of alanine aminotransferase normalization, with sustained rates of virologic control over 48 weeks.

Similar results were seen for bone mineral density. "It goes up over time, and you approach bone mineral density levels that are similar to [levels in] those who are on tenofovir alafenamide long term," Dr. Kwo said, commenting on results of the study.

The two agents are "Coke and Pepsi" in terms of efficacy, he added, noting that comparative studies showed similar efficacy on endpoints of percentage HBV DNA less than 29 IU/mL and $\log_{10}$ HBV DNA change.

Very low rates of resistance are seen with first-line therapies for chronic hepatitis B, including entecavir and tenofovir disoproxil. "We wouldn't expect (tenofovir alafenamide) to be any different, but nonetheless the surveillance has to happen," Dr. Kwo said.

Tenofovir alafenamide is not yet listed in the official recommendations of the American Association for the Study of Liver Diseases, but it is in current guidelines from the European Association for the Study of the Liver.

The published EASL guidelines provide guidance on how tenofovir alafenamide fits into the treatment armamentarium for HBV. According to the EASL recommendations, age greater than 60 years, bone disease, and renal alterations are all good reasons to use tenofovir alafenamide as first-line therapy for hepatitis B, according to Dr. Kwo.

Dr. Kwo reported disclosures related to AbbVie, Allergan, Bristol-Myers Squibb, and several other pharmaceutical companies.

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