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KARI OAKES/MDEDGE NEWS

Dr. Theresa Lee (left), Dr. Scott Ketover, AGAF, and Dr. Marc Sonenshine speak on a panel at the AGA Partners in Value meeting.

How to bring telemedicine to your GI practice

BY KARI OAKES
MDedge News

CHICAGO – Is your practice ready for telemedicine – and should you dive in?

Once you and your practice managers work through regulatory, legal, and technical details, having a robust telemedicine practice can boost patient and clinician satisfaction – and the bottom line, said Theresa Lee, MD, a gastroenterologist in private practice in Lone Tree, Colo., speaking at the 2019 AGA Partners in Value meeting.

The general field of telehealth – in which images might be shared or patients might message their care team for medication refills – is a broad term, said Dr. Lee. She explained that telemedicine is narrowly defined for Medicare and Medicaid reimbursement purposes as "two-way, real-time interactive communication between the patient and the physician or practitioner at [a] distant site ... that includes, at a minimum, audio and video equipment." This is the video visit that many

See **Telemedicine** · *page 26*

Clinicians ask FDA for continued 'discretion' to do fecal transplants

BY ALICIA AULT
Medscape Medical News

See related story on page 23.

Attendees at a public meeting on Nov. 4 gave the Food and Drug Administration conflicting views on whether the agency should continue to allow a relatively loose regulatory environment for fecal microbiota transplants (FMT) – debating the limits of "enforcement discretion" the FDA now has in place.

The question is especially relevant as use of the procedure is growing, while safety data are not being rigorously collected in all cases. The death of an immunocompromised FMT patient earlier in 2018 from an invasive bacterial infection caused by drug-resistant *Escherichia coli*, as reported by *Medscape Medical News*, is seen by some as an example of the consequences of a loose policy.

Still, the American Gastroenterological Association (AGA) presented new, unpublished follow-up data at the meeting that showed that the majority of FMT patients in a national registry had no adverse events.

Some companies developing FMT-based products argued at the meeting that the agency should impose stricter requirements, while stool banks and clinicians offering the therapy outside of clinical trials said that the current policy – in place

See **Transplants** · *page 22*

Oral budesonide effective for eosinophilic esophagitis in pivotal trial

BY BRUCE JANCIN
MDedge News

SAN ANTONIO – An investigational muco-adherent swallowed formulation of budesonide developed specifically for treatment of eosinophilic esophagitis aced all primary and secondary endpoints in a pivotal, phase 3, double-blind, placebo-controlled randomized trial, Ikuo Hirano, MD, AGAF, reported at the annual scientific meeting of the American College of Gastroenterology.

This is welcome news for patients with this chronic

See **Budesonide** · *page 17*

INSIDE

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LETTER FROM THE EDITOR:

Inner demons

Julia Brennan sings about inner demons. They just won't go away, and they don't play fair with angels. We have marveled at the miracles of fecal microbiome transplants (FMT), but this month we read about an inner demon. Two patients developed bacteremia from extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* transmitted during FMT from stool derived from a single donor. One patient, with cirrhosis, who received FMT as part of a trial to treat hepatic encephalopathy, recovered. A second patient with myelodysplastic syndrome underwent allogeneic hematopoietic stem cell transplantation and received FMT as part of a phase 2 trial. This severely immunocompromised patient succumbed to sepsis related to the *E. coli* bacteremia. Both organisms were genetically traced to the donor stool. The AGA has NIH funding to develop and maintain an FMT registry (see https://www.gastrojournal.org/article/S0016-5085[17]30088-4/pdf) so we can understand long-term risks and benefits. These rare experiences will lead to increased scrutiny and likely further FDA regulations. Gastroenterologists should be careful about choosing patients for FMT.

This month, we again feature an article about incorporating telehealth into your practice – this month's article highlights the potential for private practices to incorporate this emerging technology. There are interesting articles about treatment of eosinophilic esophagitis, acute liver failure, and postcolonoscopy interval cancers. Finally, we are cautioned about the vulnerability of our biosimilar market. This market may wither despite the great potential to reduce therapeutic costs.

Last week, I taught an undergraduate course about health care economics. After recounting current challenges, one student said, "I am a first-year medical student, what should I do?" I was caught off guard. The future is too overwhelming. As we enter the 12-month countdown to a national election, I would suggest that we continue to advocate for our patients and educate our political leaders about verifiable root causes of our major problems. Despite current antipathy to science and data, we are scientists and eventually truth will prevail. "The arc of the moral universe is long, but it bends toward justice" (Dr. Martin Luther King, Jr.).

Dr. Allen

Last week, I taught an undergraduate course about health care economics. After recounting current challenges, one student said, "I am a first-year medical student, what should I do?" I was caught off guard. The future is too overwhelming.

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

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz

Q1. What is the single most important reason for proton pump inhibitor failure in gastroesophageal reflux disease?
A. *Helicobacter pylori* infection
B. Rapid metabolism
C. Poor compliance with inappropriate administration
D. Delayed gastric emptying

Q2. A 47-year-old man with stage 5 chronic kidney disease on hemodialysis is referred to your clinic. He has genotype 1a HCV and F2 fibrosis. He wants to discuss treatment options.

What is the best advice?
A. He is not eligible for HCV therapy because of hemodialysis
B. Sofosbuvir/ledipasvir combination therapy dosed after dialysis for 12 weeks
C. Sofosbuvir/ledipasvir combination therapy for 12 weeks
D. Elbasvir/grazoprevir combination therapy for 12 weeks
E. Daily fixed-dose combination sofosbuvir/velpatasvir for 12 weeks

The answers are on page 28.

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GI & HEPATOLOGY NEWS

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Hepatitis B core–related antigen is risk factor for HCC

BY AMY KARON
MDedge News

A high level of hepatitis B core–related antigen (HBcrAg) was a complementary risk factor for hepatocellular carcinoma, according to the results of a retrospective cohort study of more than 2,600 noncirrhotic adults with untreated hepatitis B virus (HBV) infection with a median of 16 years of follow-up.

"Patients with an intermediate viral load and high levels of HBcrAg had a risk for hepatocellular carcinoma that did not differ significantly from that of patients with a high viral load. [An] HBcrAg of 10 KU/mL may serve as a novel biomarker for the management of patients with intermediate viral load in our clinical practice," wrote

Tai-Chung Tseng, MD, PhD, of National Taiwan University Hospital in Taipei and associates in Gastroenterology.

Deciding whether to start antiviral therapy is controversial for some patients with HBV infection. Typically, monitoring without treatment is recommended for patients who have both low hepatitis B surface antigen levels (less than 1,000 IU/mL) and low levels of HBV DNA (less than 2,000 IU/mL), and early antiviral therapy is recommended for patients who have high levels of HBV DNA (20,000 IU/mL or more). However, there is no clear evidence that early antiviral therapy benefits patients who have intermediate levels of HBV DNA (2,000-19,999 IU/mL) and are negative for hepatitis B e antigen. Biomarkers for risk-stratifying these patients also are lacking, the researchers noted.

'To the best of our knowledge, this is the first study to report HBcrAg level as an independent viral biomarker to stratify hepatocellular risks in a large number of patients with intermediate viral load.'

Therefore, they studied a cohort of 2,666 adults who had tested positive for hepatitis B surface antigen and were followed at National Taiwan University Hospital from 1985 through 2000. No patient had cirrhosis at baseline. In all, 209 patients developed hepatocellular carcinoma, yielding an incidence rate of 4.91 cases per 1,000 person-years.

Hepatitis B core–related antigen

Continued on following page

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Threshold for positivity affects FIT sensitivity for detecting CRC, advanced adenomas

BY AMY KARON
MDedge News

Thresholds for positivity affected the sensitivity and (to a lesser extent) the specificity of quantitative fecal immunochemical tests used in the detection of colorectal cancer, which suggests that centers should consider lowering their thresholds for positivity if they have sufficient resources to handle an increase in follow-up colonoscopies, researchers wrote in Gastroenterology.

"Additional data are needed regarding the influence of sex and age on test performance," wrote Kevin Selby, MD, of Kaiser Permanente Division of Research in Oakland, Calif., together with his associates. Additional studies also should evaluate the effect of a quantitative threshold of 10 mcg of hemoglobin per gram of feces and multiple rounds of annual testing, they added.

Fecal immunochemical tests (FITs) are recommended for colorectal cancer screening because they are diagnostically superior and are associated with higher participation rates, compared with guaiac fecal occult blood tests, the investigators noted. For screening, the optimal positivity threshold for quantitative FIT remains controversial, is likely to vary by sex and age, and also may be adjusted to reflect local health care resources. To more closely evaluate the correlates and effects of FIT cutoffs for sensitivity, the researchers searched MEDLINE, EMBASE, and the Database of Abstracts of Reviews of Effects for articles on the use of FIT for asymtomatic (screening) colorectal cancer detection in adults. This method identified 46 studies with 2.4 million participants and 6,478 detected cancers. The researchers then calculated sensitivity, speci-

Continued on following page

Quantitative fecal immunochemical tests or FITs are the most recent incarnation of screening for colorectal cancer (CRC) through the identification of occult blood in stool. Older versions of such tests were the first screening modalities shown to decrease both the incidence and mortality of CRC. FITs are much more sensitive for both CRC and advanced adenomas than are those early occult blood tests. They also are among the least costly and most easily employed CRC screening modalities. Given the quantitative nature of FITs, the question has remained as to what positivity threshold should be employed to achieve the optimal balance of sensitivity and specificity.


Dr. Ness

The current study by Selby et al. examined data from 46 studies and 2.4 million participants from 12 countries. By lowering the positivity threshold to less than 10 mcg/g from greater than 10 mcg/g but less than 20 mcg/g, the authors found the sensitivity for CRC increased from 69% to 80% and for advanced adenomas from 21% to 31%, with a trivial fall in specificity from 94% to 91%. They also found that neither sex nor age significantly altered these outcomes in the minority of studies that stratified by these demographics. These outcomes suggest that screening programs should lower the positivity threshold for FITs to less than 10 mcg/g from the current less than 20 mcg/g recommended by the U.S. Multi-Society Task Force on Colorectal Cancer Screening.

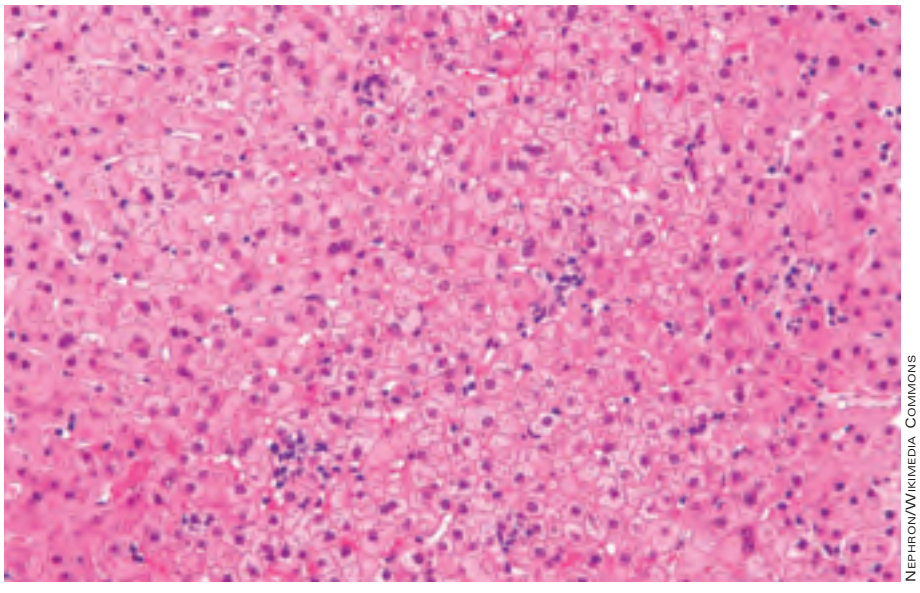
Future studies should examine more carefully demographic effects on FIT performance to determine if different positivity thresholds need to be employed in different demographic groups.

Reid M. Ness, MD, MPH, AGAF, is an associate professor in the division of gastroenterology, hepatology and nutrition, department of medicine, Vanderbilt University Medical Center and at the Veterans Affairs Tennessee Valley Healthcare System, Nashville campus. He is also an investigator in the Vanderbilt-Ingram Cancer Center. Dr. Ness has no financial relationships to disclose.

Continued from previous page

level remained an independent risk factor for hepatocellular carcinoma after accounting for age, sex, serum alanine aminotransferase level, FIB-4 index, hepatitis B e antigen status, hepatitis B genotype (B, C, or undetermined), and HBV DNA level. Compared with patients whose HBcrAg level was less than 10 KU/mL, a level of 10-99 KU/mL was associated with a nearly threefold increase in risk for hepatocellular carcinoma (HR, 2.93; 95% CI, 1.67-4.80), and this risk rose even further as HBcrAg levels increased.

In the subgroup of patients who tested negative for hepatitis B e antigen, had an intermediate HBV DNA load (2,000-19,999 IU/mL), and had a normal baseline ALT level (less than 40 U/L), a high HBcrAg level (10 KU/mL or more) was tied to a nearly fivefold greater risk for hepatocellular carcinoma (HR, 4.89; 95% CI, 2.18-10.93). This approximated the risk that is observed with high viral load (20,000 IU/mL), the researchers noted. In contrast, a low HBcrAg level was associated with a risk similar to that of minimal risk carriers (annual incidence rate, 0.10%; 95% CI, 0.04%-0.24%).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Intermediate magnification micrograph of ground glass hepatocytes are shown for chronic hepatitis B infection as seen in with a high viral load. (liver biopsy, H&E stain).

"To the best of our knowledge, this is the first study to report HBcrAg level as an independent viral biomarker to stratify hepatocellular risks in a large number of patients with intermediate viral load," the researchers commented.

Among the study limitations, 412 patients received antiviral therapy during follow-up. "This is a retrospective cohort study including Asian HBV patients with genotype B or C infection," the investigators added. "It is unclear whether this finding could be extrapolated to populations with other HBV genotype infections. Nonetheless, we had a sound cohort, as several HBsAg-related clinical findings based on our cohort have already been validated by other prospective cohort studies, implying that our data were unlikely to be biased by the study design."

Funders included National Taiwan University Hospital, the Ministry of Science and Technology, Executive Yuan in Taiwan, and National Health Research Institutes. The researchers reported having no conflicts of interest.

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SOURCE: Tseng T-C et al. Gastroenterology. 2019 Aug 27. doi: 10.1053/j.gastro.2019.08.028.

Blocking TLR9 may halt brain edema in ALF

BY WILL PASS
MDedge News

A toll-like receptor 9 (TLR9) antagonist may eventually be used to combat brain edema in acute liver failure, according to investigators.

This prediction is based on results of a recent study involving mouse models, which showed that ODN2088, a TLR9 antagonist, could stop ammonia-induced colocalization of DNA with TLR9 in innate immune cells, thereby blocking cytokine production and ensuant brain edema, reported lead author Godhev Kumar Manakkat Vijay of King's College London and colleagues.

"Ammonia plays a pivotal role in the development of hepatic encephalopathy and brain edema in acute liver failure," the investigators explained in Cellular and Molecular Gastroenterology and Hepatology. "A robust systemic inflammatory response and susceptibility to developing infection are common in acute liver failure, exacerbate the development of ammonia-induced brain edema and are major prognosticators. Experimental models have unequivocally associated ammonia exposure with astrocyte swelling and brain edema, potentiated by proinflammatory cytokines."

A robust systemic inflammatory response and susceptibility to developing infection are common in acute liver failure, exacerbate the development of ammonia-induced brain edema, and are major prognosticators.

The investigators added that, "although the evidence base supporting the relationship between ammonia, inflammation, and brain edema is robust in acute liver failure, there is a paucity of data characterizing the specific pathogenic mechanisms entailed." Previous research suggested that TLR9 plays a key role in acetaminophen-induced liver inflammation, they noted, and that ammonia, in combination with DNA, triggers TLR9 expression in neutrophils, which brought TLR9 into focus for the present study.

Along with wild-type mice, the investigators relied upon two knockout models: TLR9–/– mice, in which TLR9 is entirely absent, and LysM-Cre TLR9fl/fl mice, in which TLR9 is absent from lysozyme-expressing cells (predominantly neutrophils and macrophages). Comparing against controls, the investigators assessed cytokine production and brain edema in each type of mouse when intraperitoneally injected with ammonium acetate (4 mmol/kg). Specifically, 6 hours after injection, they measured intracellular cytokines in splenic macrophages, CD8+ T cells, and CD4+ T cells. In addition, they recorded total plasma DNA and brain water, a measure of brain edema.

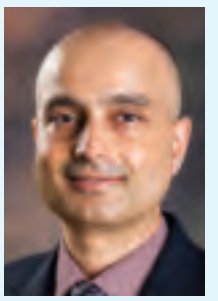
Following ammonium acetate injection, wild-type mice developed brain edema and liver enlargement, while TLR9–/– mice and control-injected mice did not. After injection, total plasma DNA levels rose by comparable magnitudes in both wild-type mice and TLR9–/– mice, but did not change in control-injected mice, suggesting that ammonium-acetate injection was causing a release of DNA, which was binding with TLR9, resulting in activation of the innate immune system.

This hypothesis was supported by measurements of cytokines in T cells and splenic macrophages, which showed that wild-type mice had elevations of cytokines, whereas knockout mice did not. Further experiments showed that LysM-Cre TLR9fl/fl mice had similar outcomes as TLR9–/– mice, highlighting that macrophages and neutrophils are the key immune cells linking TLR9 activation with cytokine release, and therefore brain edema.

To ensure that brain edema was not directly caused by the acetate component of ammonium acetate, or acetate's potential to increase pH, researchers injected a different set of wild-type mice with sodium acetate adjusted to the same pH as ammonium acetate. This had no impact on cytokine production, brain-water content, or liver-to-body weight ratio, confirming that acetate was not responsible for brain edema while providing further support for the role of TLR9.

Finally, the investigators treated wild-type mice immediately after ammonium acetate injection with the TLR9 antagonist ODN2088 (50 mcg/mouse). This treatment halted cytokine production, brain edema, and hepatocyte swelling, which was reversed with the TLR9 antagonist ODN2088.

These data add to the growing literature about the interaction between immune dysfunction and brain diseases such as schizophrenia, autism, depression, and multiple sclerosis. However, further studies in models of brain edema with concomitant liver failure, which are closer to the human disease process, are needed. This exciting investigation of neuroimmune regulation of brain edema could set the basis for new therapeutic options for the prevention and treatment of this feared complication of acute liver failure.


Dr. Bajaj

Jasmohan S. Bajaj, MD, AGAF, is professor in the division of gastroenterology, hepatology, and nutrition at Virginia Commonwealth University, Richmond. He reported no conflicts of interest.

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ficity, numbers of detected cancers, advanced adenomas, and positive test results at positivity thresholds of up to 10 mcg, 10-20 mcg, 20-30 mcg, and more than 30 mcg of hemoglobin per gram of feces. They also examined subgroups stratified by sex and age.

The pooled sensitivity for the detection of colorectal cancer rose from 69% (95% confidence interval, 63%-75%) at a positivity threshold of more than 10 and up to 20 mcg of hemoglobin per gram of feces, to 80% at a positivity threshold of 10 mcg or less of hemoglobin per gram of feces. "At these [same] threshold values, sensitivity for detection of advanced adenomas increased from 21% (95% CI, 18%-25%) to 31% (95% CI, 27%-35%), whereas specificity decreased from 94% (95% CI, 93%-96%) to 91% (95% CI, 89%-93%)," the researchers wrote.

Only three studies stratified results by sex, and these found no statistical difference in pooled sensitivity for detecting colorectal cancer among men (77%) versus women (81%). Age, too, was stratified in only three studies and did not significantly correlate with sensitivity. "More research is needed to precisely establish FIT thresholds for each sex and age subgroup," the researchers said.

The National Cancer Institute and the Swiss Cancer Research Foundation provided funding. The investigators reported having no conflicts of interest.

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SOURCE: Selby K et al. Gastroenterology. 2019 Aug 22. doi: 10.1053/j.gastro.2019.08.023.

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†Based on a post hoc analysis of 2-week data from 2 previously published identical phase IV, multicenter, randomized, double-blind, placebo-controlled trials that demonstrated efficacy and safety of esomeprazole 20 mg once daily in the morning in subjects with sleep disturbances due to reflux and frequent nighttime heartburn.

‡Complete resolution of heartburn was defined as 7 consecutive days without heartburn.

§First resolution defined as a study day when patients recorded "NO" sleep disturbances due to frequent heartburn on daily diary card.

References: 1. National Sleep Foundation. Ease heartburn at bedtime. https://sleep.org/articles/ease-heartburn-bedtime/. Accessed August 6, 2018. **2.** Johnson DA, Le Moigne A, Hugo V, Nagy P. Rapid resolution of sleep disturbances related to frequent reflux: effect of esomeprazole 20 mg in two randomized, double-blind, controlled trials. *Curr Med Res Opin.* 2015;31(2):243-250.

Pfizer Consumer Healthcare

09/18

Daily aspirin might cut risk of fibrosis progression

BY AMY KARON
MDedge News

Taking daily aspirin may help keep nonalcoholic fatty liver disease from progressing to liver fibrosis and nonalcoholic steatohepatitis (NASH), suggest the results of a prospective study of 361 adults.

Previously, preclinical evidence had linked aspirin to fibrogenesis prevention in fatty liver disease, but this is the first report of a prospective study to do so. Daily aspirin use "was associated with less severe histologic features of NAFLD (nonalcoholic fatty liver disease) at study enrollment and with significantly lower risk for advanced fibrosis over time in a duration-dependent manner," wrote Tracey G. Simon, MD, MPH, and her associates. Their report is in Clinical Gastroenterology and Hepatology.

Importantly, the link between aspirin and decreased risk of fibrosis progression seemed to depend on duration of use, with the greatest benefit seen with 4 years or more of use.

The study comprised 361 adults with biopsy-confirmed NAFLD who were enrolled in the Massachusetts General Hospital NAFLD Repository between 2006 and 2015. At baseline, 151 individuals were already on daily aspirin, usually to reduce the primary (54%) or secondary (30%) risk of cardiovascular disease. Median duration of aspirin use was 2.5 years. After a median 7.4 years of follow-up (which was similar between aspirin users and nonusers), daily aspirin use was associated with significantly lower odds of NASH (adjusted odds ratio, 0.68; 95% confidence interval, 0.37-0.89) and fibrosis (aOR, 0.54; 95% CI, 0.31-0.82).

The researchers did not find a similar protective effect for nonsteroidal anti-inflammatory drugs other than aspirin (adjusted hazard ratio for advanced fibrosis, 0.93; 95% CI, 0.81–1.05). This might be because of differences between how aspirin and nonaspirin NSAIDs affect COX isoforms – aspirin does so irreversibly, while other NSAIDs have a reversible effect, they added. "Nonaspirin NSAIDs also disrupt the intestinal barrier, increasing delivery of proinflammatory cytokines to the liver," they wrote. "Finally, aspirin uniquely modulates bioactive lipids by stimulating the biosynthesis of pro-resolving mediators and inhibiting proinflammatory lipids, which in turn may prevent progressive liver damage."

In this study, a single-blinded hepatopathologist interpreted baseline liver biopsy specimens, and patients were followed every 3-6 months with clinical examinations and serial calculations of FIB-4, NFS, and APRI scores. All patients were followed for at least a year. Patients were classified as users of nonaspirin NSAIDs if they reported using an NSAID besides aspirin at least twice weekly, or if they had been prescribed drugs such as ibuprofen, naproxen, ketoprofen, diclofenac, or indomethacin.

In a longitudinal analysis of the 317 patients who had early-stage (F0-2) fibrosis at baseline, 86 developed new-onset advanced fibrosis over a median of 3,692 person-years, the researchers said. In all, 26 individuals developed hepatic decompensation and 18 patients died, including 8 from liver-related causes. Importantly, the link between aspirin and decreased risk of fibrosis progression seemed to depend on duration of use (adjusted *P* trend = .026), with the greatest benefit seen with 4 years or more of use (aHR, 0.50; 95% CI, 0.35-0.73). Although subgroup analyses were limited by lack of power, daily aspirin use was associated with a 36% lower odds of incident advanced fibrosis among the 72 study participants who had paired biopsy samples, even after accounting for the effect of age, sex, baseline fibrosis stage, and time between biopsies (aOR, 0.64; 95% CI, 0.50-0.80).

"Our findings add to the growing literature supporting the potential hepatoprotective effects of aspirin in NAFLD," the researchers concluded. "Research to uncover the mechanisms by which aspirin might prevent fibrogenesis could help develop urgently needed antifibrotic therapies for NAFLD."

Funders included the National Institutes of Health and the AASLD Foundation. The investigators reported having no conflicts of interest.

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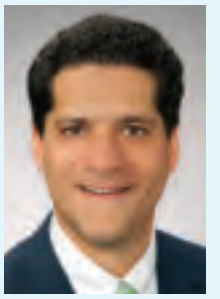
SOURCE: Simon TG et al. Clin Gastroenterol Hepatol. 2019 May 8. doi: org/10.1016/j.cgh.2019.04.061.

Slowing, preventing, or reversing fibrogenesis in patients with NAFLD remains an unmet need. Lifestyle interventions are beneficial to this population but challenging because of concerns with adherence and sustainability, thus, favoring pharmacologic interventions. The study by Simon et al. provides initial prospective evidence of the role of aspirin in reducing progression of fibrosis. In a thoughtful design, authors showed both cross-sectional and longitudinal associations of reduced risk for progressed fibrosis among aspirin users, all with biological coherence and while accounting for various confounding factors. Although the accuracy of blood-based noninvasive assessment of liver fibrosis (by FIB-4, NFS, and APRI) to determine progression of fibrosis in NAFLD has moderate accuracy at its best, the relatively high FIB-4 cutoff value used by the authors and their sensitivity analyses (including liver biopsy and combinations of blood-based markers combined endpoints) bring certainty to their results. However, before we can start prescribing aspirin to halt progression of fibrosis in NAFLD, larger and adequately powered studies are needed. Caution with the use of aspirin as prophylaxis for atherosclerotic cardiovascular disease (ASCVD) is now advised, based on results from large clinical trials (i.e., ASCEND). NAFLD patients represent a particular population with both a high ASCVD risk and a high risk for gastrointestinal bleeding, and it is unclear what the number needed to treat or to harm would be without confirmatory studies. An "NAFLD polypill" including a combination of drugs addressing multiple metabolic pathways (e.g. aspirin, a statin, and vitamin E) might well tip the scale in favor of improved clinical outcomes, a concept recently shown as beneficial for ASCVD prevention in the PolyIran study. Until then, properly weighing the use of prophylactic aspirin in patients with NAFLD and adhering to standard recommendations is advised.



Dr. Duarte-Rojo

Andres Duarte-Rojo, MD, PhD, is associate professor of medicine, division of gastroenterology, hepatology, and nutrition at the University of Pittsburgh Medical Center, and Pittsburgh Liver Research Center. He received research support from Echosens, USA.

Continued from page 6

tokine production, inflammation, and brain edema, strongly supporting the link between these ammonia-induced processes and TLR9 activation.

"These data are well supported by the findings of Imaeda et al. (J Clin Invest. 2009 Feb 2. doi: 10.1172/JCI35958), who in an acetaminophen-induced hepatotoxicity model established that inhibition of TLR9 using ODN2088 and IRS954, a TLR7/9 antagonist, down-regulated proinflammatory cytokine release and reduced mortality," the investigators wrote. "The amelioration of brain edema and cytokine production by ODN2088 supports exploration of TLR9 antagonism as a therapeutic modality in early acute liver failure to prevent the development of brain edema and intracranial hypertension."

The study was funded by the U.K. Institute of Liver Studies Charitable Fund and the National Institutes of Health. The investigators reported no conflicts of interest.

ginews@gastro.org

SOURCE: Vijay GKM et al. Cell Mol Gastroenterol Hepatol. 2019 Aug 8. doi: 10.1016/j.jcmgh.2019.08.002.

Postcolonoscopy CRCs had unique features

BY AMY KARON
MDedge News

Postcolonoscopy colorectal cancers were more likely to arise in the proximal colon and to show microsatellite instability, according to the results of a retrospective population-based study of 168 adults with incident colorectal cancers.

In all, 64% of postcolonoscopy colorectal cancers were located in the proximal colon, compared with 44% of detected colorectal cancers (P = .016), reported Niloy Jewel Samadder, MD, of the University of Utah in Salt Lake City, together with his associates. Furthermore, microsatellite instability (MSI) was detected in 32% of postcolonoscopy colorectal cancers, versus 13% of detected colorectal cancers (P = .005). These findings may point to differences in the underlying biology of postcolonoscopy colorectal cancers and detected colorectal cancers, they said. Studies are needed "to determine if postcolonoscopy cancers arise through a specific genetic pathway that may accelerate neoplastic progression," they wrote in Clinical Gastroenterology and Hepatology.

Postcolonoscopy colorectal cancers are a "small but clinically important subset of colorectal cancers" that are diagnosed after the patient has a colonoscopy in which no cancer is detected, the researchers noted. These cancers have an estimated global prevalence ranging from 3% to 9% and an estimated pooled prevalence of 3.7% (Am J Gastroenterol. 2014;109:1375-89). Risk factors for postcolonoscopy colorectal cancers include low adenoma detection rates, rural facilities, and care by physicians who are not gastroenterologists. However, tumor-specific and patient-specific factors, including location within the colon and superior survival, compared with detected cancers, raises the possibility of underlying molecular differences related to tumorigenesis, the researchers said.

To investigate this idea, they retrospectively analyzed data from residents of Utah between 50 and 80 years old who had a colonoscopy between, Feb. 15, 1995, and Jan. 31, 2009, at one of two large clinical facilities in Utah (Intermountain Healthcare or the University of Utah Health Sciences). Using a state population-based database, they merged medical information from these patients with cancer histories from the Utah Cancer Registry. This enabled them to compare all 84 postcolonoscopy colorectal cancers (defined as those detected within 6-60 months of colonoscopy) with tissue available for analysis with 84 detected colorectal cancers (detected within 6 months of a colonoscopy).

In the multivariable analysis, MSI was the only molecular feature that was significantly more frequent in postcolonoscopy versus detected colorectal cancers (odds ratio, 4.20; 95% confidence interval, 1.58-11.14). However, postcolonoscopy colorectal cancers were significantly more likely to be early stage (86% versus 69% for detected colorectal cancers; P = .040). Five-year survival did not significantly differ between the groups.

"The molecular signatures of postcolonoscopy colorectal cancers in our study overlap with those of sporadic MSI and serrated pathways, suggesting these mechanisms play a disproportionate role in postcolonoscopy colorectal cancers," the researchers said. "Additional studies are needed to determine whether these postcolonoscopy colorectal cancers arise through a familial cancer pathway and/or serrated neoplastic pathway of sporadic lesions.

Funders included the American College of Gastroenterology, the National Cancer Institute, the Huntsman Cancer Foundation, the University of Utah, and the Utah Department of Health. Dr. Samadder reported consulting relationships with Cancer Prevention Pharmaceuticals and Janssen Research and Development. The other researchers reported having no conflicts of interest.

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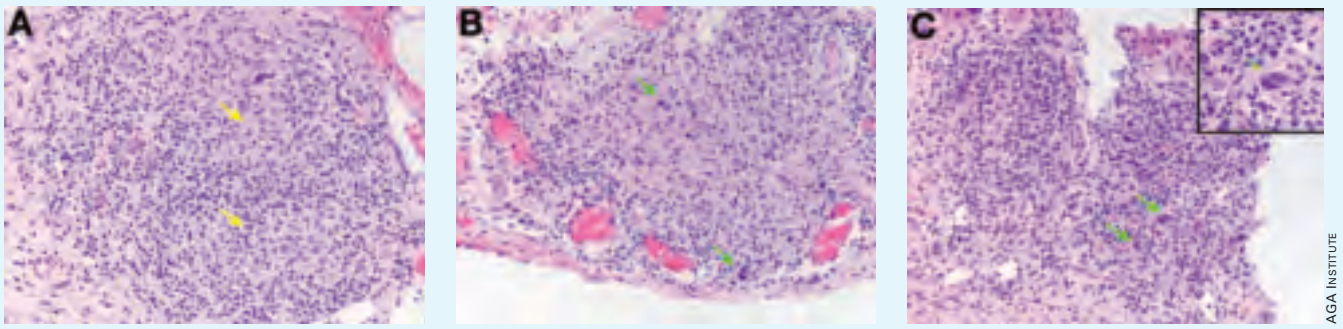
SOURCE: Samadder NJ et al. Clin Gastroenterol Hepatol. 2019 Mar 28. doi: 10.1016/j.cgh.2019.02.040.

CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

By Ruhail Kohli, MD, Hubert H. Fenton, MD, and Lisa M. Forman, MD. Published previously in Gastroenterology (2018;154[6]:1588-9).



A 68-year-old woman with a history of pulmonary sarcoidosis, chronic lymphocytic thyroiditis, hyperlipidemia, and osteopenia was evaluated for elevated liver enzymes. Liver enzymes were found to be elevated 7 months earlier. Routine laboratory tests showed aspartate aminotransferase of 57 U/L (upper limit, 39 U/L), alanine aminotransferase of 54 U/L (upper limit, 52 U/L), alkaline phosphatase of 175 U/L (upper limit, 117 U/L), and total bilirubin of 0.5 mg/dL (upper limit, 1.3 mg/dL). She was on prednisone 5 mg/d, methotrexate 17.5 mg/wk, and atorvastatin 40 mg/d. Methotrexate and atorvastatin were stopped and prednisone increased to 10 mg/d.

Two months later, repeat laboratory tests showed aspartate aminotransferase of 213 U/L, alanine aminotransferase of 93 U/L, alkaline phosphatase of 1,472 U/L, and total bilirubin of 6.0 mg/dL. The initial ultrasound scan was normal. On further assessment, she complained of malaise, weight loss, shortness of breath, dry eyes, dry mouth, and insomnia. She denied any significant alcohol use. No new medications or supplements were started recently. Vital signs were normal. Physical examination was unremarkable. Viral hepatitis serologies were negative. Antinuclear antibody, anti–smooth muscle antibody, and antimitochondrial antibody were negative. She had a magnetic resonance cholangiopancreatography, which showed splenomegaly but was otherwise unremarkable. She had a liver biopsy (Figure A), which showed nonnecrotizing granulomas (yellow arrows) with a chronic inflammatory lymphocytic infiltrate.

Given these findings, prednisone was increased to 20 mg. In the interim, the patient was admitted with acute acalculous cholecystitis. She had a laparoscopic cholecystectomy and an intraoperative liver biopsy. She developed respiratory failure postoperatively and was transferred to intensive care. Stress dose steroids and antibiotics were initiated. Laboratory tests showed a white blood cell count of 13.8×10^9/L, hemoglobin of 9.4 g/dL, platelets at 223×10^9/L, aspartate aminotransferase of 97 U/L, alanine aminotransferase of 63 U/L, alkaline phosphatase of 1,607 U/L, total bilirubin of 5.8 mg/dL (direct 3.3), and albumin of 2.4 g/dL. Pathology from the gallbladder (Figure B) and the intraoperative liver biopsy (Figure C) showed cells pathognomonic for the condition (green arrows).

On the basis of these findings, what is the final diagnosis?

The diagnosis is on page 13.

What's new with the liver and the microbiome

BY JASMOHAN BAJAJ, MD, AGAF

There is a growing interest in the gut-brain-liver axis and the relationship between the gut microbiome and liver diseases such as nonalcoholic fatty liver disease (NAFLD). I want to highlight three recent articles with clinical implications for those with an interest in these connections.

This first paper generated a lot of media coverage recently. It is a fascinating story that started with a single patient who presented with severe nonalcoholic steatohepatitis and autobrewery syndrome – which caused the patient to have extremely high blood alcohol concentrations despite an alcohol-free (but high-carbohydrate) diet. The authors went on to study the broader implications of the gut microbiota in patients with NAFLD.

• Yuan J et al. Fatty liver disease caused by high-alcohol-producing *Klebsiella pneumoniae.* Cell Metab. 2019 Oct 1;30(4):675-88.e7. doi: 10.1016/j.cmet.2019.08.018. Epub 2019 Sep 19.

Key takeaway: This translational study found that the gut microbiomes of Chinese patients with NAFLD, when compared to healthy patients, had significantly higher levels of high-alcohol-producing strains of *Klebsiella pneumoniae* (Kpn).

More details: When Kpn were isolated from human subjects and transplanted to mice, the mice developed NAFLD. Mice who received Kpn transplants also had higher blood alcohol levels when given a glucose infusion. These results suggest that endogenous alcohol produced by the gut microbiota could help drive NAFLD and that assessing blood alcohol concentration after a glucose infusion should be studied further as a potential biomarker for the diagnosis and treatment of NAFLD.

Important caveats: Only 60% of patients in the study had elevated Kpn in their gut microbiomes and only Chinese patients were studied, so these results must be tested in more diverse racial, ethnic, and geographic populations for broader applicability. (Note that Zhu et al. have shown this phenomenon from other taxa belonging to Enterobacteriaceae in pediatric NASH.)

The next two papers focus on hepatic encephalopathy (HE), a very prevalent neurocognitive disorder that is epidemic in patients with chronic liver disease and can also occur as part of acute liver failure. HE can have an overt acute form (OHE), characterized by altered mental status that is prone to recurrence even after the patient returns to their baseline and a more common minimal or subclinical form (MHE). MHE is associated with poor clinical and psychosocial outcomes, is treatable, but is difficult to diagnose because of logistic concerns regarding testing strategies. The first paper compares the gut microbiomes of patients with cirrhosis but with or without OHE during hospitalizations, including associations with mortality and recurrences after 1 year. The second paper, from my own group, looks at the gut and salivary microbiomes as potential signatures for diagnosing cognitive function in patients with HE.

• Sung CM et al. Predicting clinical outcomes of cirrhosis patients with hepatic encephalopathy from the fecal microbiome. Cell Mol Gastroenterol Hepatol. 2019;8(2):301-18.e2. doi: 10.1016/j.jcmgh.2019.04.008. Epub 2019 Apr 18.

Key takeaway: This study tracked the gut microbiomes of patients with acute episodes of overt hepatic encephalopathy (AHE) throughout the treatment and recovery process as well as the outcomes of these patients 1 year after they were treated at the emergency unit. Importantly, in-

Continued on following page

Dr. Anil Rustgi and Dr. Raymond DuBois elected to National Academy of Medicine

Anil Rustgi, MD, AGAF, and Raymond DuBois, MD, PhD, AGAF, were elected to the National Academy of Medicine, considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

Dr. Rustgi

Dr. DuBois

Share your congratulations with both Dr. Rustgi and Dr. DuBois on the AGA Community.

Dr. Rustgi is recognized for illuminating the importance of GI cancers, genomics, and genetics and demonstrating that p120-catenin, part of the adherens junctions, is a tumor suppressor gene in cancers and the first to link p120-catenin to mesenchymal-epithelial transition (MET) in tumor metastasis, advancing therapeutic opportunities.

Dr. Rustgi is Irving Professor of Medicine and director of the Herbert Irving Comprehensive Cancer Center, and associate dean of oncology, department of medicine, Vagelos College of Physicians and Surgeons at Columbia University, New York.

Dr. DuBois is recognized for discovering the critical and mechanistic role of prostaglandins (PGs)/cyclooxygenase in colon cancer and its malignant progression, elucidating the role of PGs in the tumor microenvironment, and spearheading the now common use of drugs for human cancer prevention that target the PG pathway, like aspirin and other NSAIDs.

Dr. DuBois is dean of the College of Medicine, and professor of biochemistry and medicine at The Medical University of South Carolina, Charleston.

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GI society update on MOC reform

Our work was suspended when ABIM announced the creation of a new longitudinal assessment option for maintenance of certification across all specialties.

GI society leaders are in touch with ABIM. Here's an update on what we know:

- The ABIM Board of Directors committed to evolve its program to provide a longitudinal assessment option for Maintenance of Certification (MOC), offering a self-paced pathway for physicians to acquire and demonstrate ongoing knowledge. The traditional, long-form assessment will also remain an option, as some physicians have expressed a preference for a point-in-time exam taken less frequently.

Our next steps include seeking clarity from ABIM including:

1. The milestones in the process to create the new pathway.

2. When the new pathway will be available to diplomates.

3. Consideration and integration of the GI societies' principles in the development of the new pathway for recertification, including:

a. MOC needs to be simpler, less intrusive, and less expensive.

b. We continue to support alternatives to the high-stakes, every-10-year recertification exam.

c. We do not support single-source or time-limited assessments, as they do not represent the current realities of medicine in the digital age.

d. We support the concept that, for the many diplomates who specialize within certain areas of gastroenterology and hepatology, MOC should not include high-stakes assessments of areas in which the diplomate may not practice.

e. We support the principles of lifelong learning, as evidenced by ongoing CME activities, rather than lifelong testing.

4. The role the GI societies, as representatives for thousands of U.S. members who are ABIM diplomates, play in the creation and implementation of the new pathway.

AASLD, ACG, AGA and ASGE want to be fully informed and fully respected partners in an endeavor that touches upon one of the toughest challenges facing our members and the single issue we hear about most often requesting our help.

We will continue to update our members as we learn the answers to these questions from ABIM.

Together, our first priority on the MOC issue remains ensuring that GI diplomates have a pathway for recertification that meets your needs.

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Continued from previous page

creased *Lactobacillus* during the AHE stage was significantly associated with patient mortality 1 year later.

More details: The investigators compared the gut microbiomes of emergency room patients with cirrhosis and AHE versus outpatients with compensated cirrhosis without HE, advanced stages of cirrhosis without HE, and healthy individuals. They found that several genera were significantly more abundant in patients with AHE: Veillonella, Clostridium XI, Prevotella, and Enterococcus. *Veillonella parvula* was the most prevalent species in patients with AHE. The authors concluded that specific microbiota are associated with the disease progression of HE and that certain microbiota could be further explored as probiotic treatments to suppress HE in susceptible patients.

Important caveats: We know that strains of microbiota within the same species can have dramatically different effects, and this study does not explore the gut microbiota to the strain-specific level. The authors also acknowledged that their results conflict with other recent studies that showed no difference in the gut microbiota between cirrhosis patients with and without HE. Clearly, there are more studies that need to be done before we can develop meaningful clinical diagnostics or interventions based on this study and other related studies.

• Bajaj JS et al. Specific gut and salivary microbiota patterns are linked with different cognitive testing strategies in minimal hepatic encephalopathy. Am J Gastroenterol. 2019 Jul;114(7):1080-90. doi: 10.14309/ajg.0000000000000102.

Key takeaway: This study of nearly 250 patients found unique signatures of gut and salivary microbiota in cirrhotic patients with MHE and found specific taxa that were associated with normal cognition regardless of modality of testing used to diagnose MHE.

More details: The investigators found that Lactobacillaceae were higher in both the gut and salivary microbiomes of cirrhosis patients with MHE, even in patients not on lactulose therapy. In contrast, patients without MHE had higher levels of Lachnospiraceae. Independent of clinical variables, *Lachnospiraceae genera* (including Ruminococcus and Clostridium XIVb) were associated with good cognitive function. These results could inform future cognitive testing strategies for MHE. MHE testing was performed using three separate strategies (app based, computer based, and paper-pencil based) and specific microbiota were associated with normal cognition regardless of which testing strategy was used.

Important caveats: These studies were limited to a U.S. regional population of patients and should be repeated in more diverse patient populations before the results are generally applied to all patients with MHE.

Dr. Bajaj is a professor in the department of internal medicine, division of gastroenterology, hepatology, and nutrition, Virginia Commonwealth University, Richmond, and a member, AGA Center for Gut Microbiome Research and Education Scientific Advisory Board.

Meet Rep. Donald Payne Jr. – A staunch advocate for increasing access to colorectal cancer screening

Rep. Donald Payne Jr., D-N.J., has been representing the 10th congressional district of New Jersey which includes the Newark area and the thriving life-sciences community in the region since 2012. Rep. Payne ran to serve in the seat that his father, the late Rep. Donald M. Payne, D-N.J., held for 11 terms until his untimely death in March 2012. The elder Payne succumbed to colon cancer 1 month after his initial diagnosis, and Rep. Payne has made it his personal mission since assuming his father's seat to increase awareness of colorectal cancer screenings. In fact, shortly after entering office, Rep. Payne wrote an op-ed with AGA member Carla Ginsburg, MD, MPH, AGAF, on the importance of screening, relaying in deeply personal terms the cost of not getting screened.

Rep. Payne also made it a top priority to push national awareness of colon cancer screening beyond the halls of Congress. To that end, Rep. Payne successfully lobbied the Obama administration in 2014 to designate March as National Colorectal Cancer Awareness Month – the first colorectal cancer presidential proclamation in over a decade.


Rep. Payne

The presidential proclamation was subsequently reissued in both 2015 and 2016 by the Obama administration and in 2018 and 2019 by the Trump administration. Additionally, Rep. Payne introduces a resolution in the House of Representatives every year to designate March as National Colorectal Cancer Awareness Month in an effort to further promote awareness and educational activities of colorectal cancer screening in the chamber.

Most importantly, Rep. Payne is the lead champion of legislative efforts in the House to increase access to colorectal cancer screenings. Specifically, Rep. Payne is the lead sponsor of H.R. 1570, the Removing Barriers to Colorectal Cancer Screening Act, legislation that has been one of AGA's top policy priorities. The legislation, which enjoys broad bipartisan support with over 300 cosponsors in the House, would correct the Medicare beneficiary coinsurance issue when a screening colonoscopy becomes therapeutic. He also is a strong supporter of biomedical research funding, noting in an op-ed with former Rep. Charlie Dent, R-Pa., that "scientists need stable, consistent, and robust funding to ensure that we can continue ... breakthroughs for the colorectal cancer community and beyond."

AGA looks forward to continuing to work with Rep. Payne and his office in the 116th Congress on these critical issues and on policies affecting our patients and the field of gastroenterology.

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Inside Dr. Swathi Eluri's journey to physician-scientist

Inspired by her father, who was diagnosed with inflammatory bowel disease (IBD), Swathi Eluri, MD, spent time during her college days at the University of North Carolina (UNC), Chapel Hill, in a GI basic science lab hoping to better understand this condition. This experience was pivotal for Dr. Eluri – she recognized her passion for research and began her journey to physician-scientist.

Dr. Eluri

After a stint at John Hopkins Hospital in Baltimore for her medical degree and residency, Dr. Eluri returned to UNC Chapel Hill for her GI fellowship, where she remains today as an assistant professor of medicine in the division of gastroenterology and hepatology. Dr. Eluri's research is focused on increasing early detection of esophageal cancer, to allow for earlier and more effective treatment. The AGA Research Foundation was proud to support Dr. Eluri's work with a 2018 AGA Research Scholar Award.

Learn more about Dr. Swathi Eluri's inspiring career by visiting:

aga research foundation

https://www.gastro.org/news/inside-dr-swathi-eluris-journey-to-physician-scientist.

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Help AGA build a community of investigators through the AGA Research Foundation.

Your donation to the AGA Research Foundation can fund future success stories by keeping young scientists working to advance our understanding of digestive diseases. Make your year-end donation today at www.gastro.org/donateonline.

Top AGA Community patient cases

Physicians with difficult patient scenarios regularly bring their questions to the AGA Community (https://community.gastro.org) to seek advice from colleagues about therapy and disease management options, best practices, and diagnoses.

In case you missed it, here are the most popular clinical discussions shared in the forum recently:

1. **Severe lower GI bleed (http://ow.ly/iTrS30pOKaP)** – A 15-year-old male patient was sent to the ER with severe lower GI bleed after a general physical exam revealed he was experiencing hypotension and tachycardia. The GI community discusses diagnostic possibilities for severe lower GI bleed at such young age and management options.

2. **Refractory nausea and vomiting in a transgender patient (http://ow.ly/Di9C30pOKbq)** – In this case of a 45-year-old transgender male-to-female patient, the community deliberates on several clinical issues, including a nonbinary gender option on patient identification forms, treatment options for the patient, and if hormonal therapy is contributing to GI symptoms.

aga community

3. **Multidisciplinary guidelines (http://ow.ly/BtUK30pOKC8)** – Are multidisciplinary guidelines with related specialty societies "the need of the hour" or too rare and short-lived for the effort?

Also in the forum: The AGA Clinical Practice Updates Committee is soliciting topics for future clinical expert review and commentaries commissioned by AGA. Share your ideas with the GI community (http://ow.ly/siV930pOJS1).

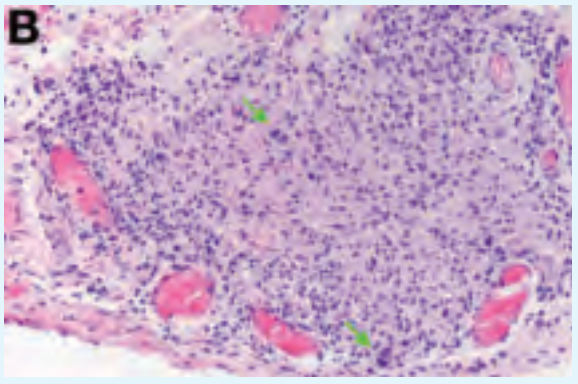
Access these clinical cases and more discussions at https://community.gastro.org/discussions.

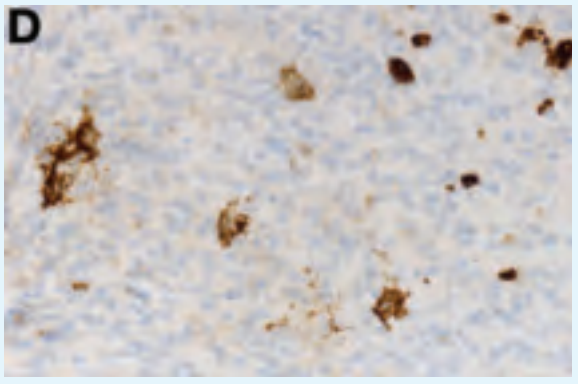
The diagnosis

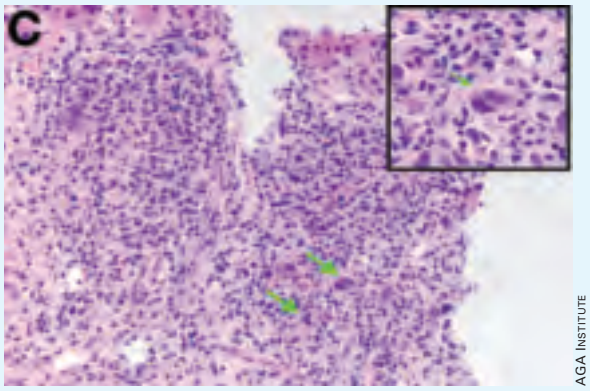
Answer to: "What is your diagnosis?" on page 9: Hodgkins lymphoma of the liver

The gallbladder (Figure B) as well as the intraoperative liver biopsy (Figure C; insert showing cells under higher power) showed nonnecrotizing granulomas along with scattered infiltration by atypical large cells morphologically consistent with Hodgkin-Reed-Sternberg cells in a lymphoid background (Figures B, C, green arrows). Immunohistochemistry showed these were positive for CD30 (Figure D, liver biopsy), weakly positive for PAX5, and negative for CD15, CD20, CD79a, and ALK-1. Given the pathologic findings, the patient was diagnosed with Hodgkins lymphoma.

The patient had a history of mediastinoscopy and lymph node biopsy in the past at an outside hospital with reported noncaseating granulomas and no other abnormalities; those slides could not be obtained for independent review. Primary lymphomas of the liver are exceedingly rare, but advanced lymphoma can have liver involvement.[1] Hodgkins lymphoma of the liver is extremely uncommon.[2] It can present with fever, hepatomegaly, and jaundice.[1] The diagnostic yield of a liver biopsy ranges from 5% to 10% depending on core versus wedge biopsy.[1] Pathologically, there is portal inflammation and atypical histiocytic aggregates but Hodgkin-Reed-Sternberg cells are required for diagnosis. These cells stain positive for CD15 and CD30 in around 80% of cases.[3] Lymphoma should remain in the differential when granulomas are seen in the liver biopsy. Our patient clinically decompensated by the time the diagnosis was confirmed. The family decided not to pursue aggressive treatment in hospital and the patient was discharged home, where she expired.







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Amneal Pharma issues recall for ranitidine products

BY LUCAS FRANKI
MDedge News

Amneal Pharmaceuticals has announced a voluntary recall for both ranitidine tablets and ranitidine syrup because of potential *N*-nitrosodimethylamine (NDMA) levels above Food and Drug Administration–allowed cutoffs, according to an FDA MedWatch alert.

NDMA, a probable human carcinogen, has been found in several different ranitidine products since an initial FDA announcement in September 2019. Ranitidine, a histamine$_2$ receptor blocker, is indicated for multiple conditions, including treatment and prevention of ulcers of the stomach and intestines and treatment of gastroesophageal reflux disease.

The affected ranitidine products being recalled by Amneal include 60-, 100-, 180-, 500-, and 1,000-count 150-mg tablets; 30-, 100-, 250-, and 1,000-count 300-mg tablets; and a 15-mg/mL syrup. The manufacturer has not received any reports of adverse events confirmed to be directly related to the recall.

Consumers should contact their physicians or health care providers if they have experienced any problems that may be related to the use of this drug product, the FDA said. Adverse reactions or quality problems can be reported to Amneal Drug Safety by phone at 1-877-835-5472.

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Drug reduced eosinophil count

Budesonide *from page 1*

immune-mediated disease, for which no Food and Drug Administration–approved drug therapy exists yet.

"This is the first phase 3 trial to demonstrate efficacy using the validated Dysphagia Symptom Questionnaire, the first completed phase 3 trial of any medical therapeutic for eosinophilic esophagitis, and the largest clinical trial for eosinophilic esophagitis conducted to date," declared Dr. Hirano, professor of medicine at Northwestern University in Chicago.

This was a 12-week induction therapy study including 318 adolescents and adults randomized 2:1 to 2 mg of budesonide oral suspension (BOS) or placebo twice daily. Patients were instructed not to eat or drink anything for 30 minutes afterward to avoid washing away the medication.

This was a severely affected patient population with high-level inflammatory activity: Their mean baseline peak eosinophil count was 75 cells per high-power field, well above the diagnostic threshold of 50 eosinophils per high-power field. In keeping with a requirement for study participation, all patients had failed to respond to at least 6 weeks of high-dose proton pump inhibitor therapy. They also had to experience solid-food dysphagia on at least 4 days per 2 weeks. More than 40% of subjects had previously undergone esophageal dilation.

One coprimary endpoint addressed histologic response, defined as 6 or fewer eosinophils per high-power field after 12 weeks of double-blind treatment. The histologic response rate was 53% in the BOS group and 1% in placebo-treated controls.

The other coprimary endpoint was symptom response as defined by at least a 30% reduction from baseline in the Dysphagia Symptom Questionnaire score. This was achieved in 53% of patients on BOS and 39% of controls.

The prespecified key secondary endpoint was the absolute reduction in Dysphagia Symptom Questionnaire score through week 12. From a mean baseline score of 30 out of a possible 84, the swallowed steroid recipients experienced a mean 13-point improvement, compared with a 9.1-point improvement for those on placebo.

The topical budesonide group also did significantly better than placebo in terms of all other secondary endpoints. Endoscopic improvement as reflected in the mean Eosinophilic Esophagitis Reference Score was greater in the BOS group by a margin of 4 versus 2.2 points. A high-bar histologic response rate of no more than a single eosinophil per high-power field at week 12 was achieved in one-third of the BOS group and zero controls. The overall peak eosinophil count from baseline to week 12 dropped by an average of 55.2 cells per high-power field in the budesonide group, compared to a 7.6-eosinophil decrease in controls. And the proportion of patients with no more than 15 eosinophils per high-power field at week 12 was 62% with BOS, compared with 1% with placebo.

Treatment-emergent adverse events were similar in the two study arms and were mild to moderate in severity. Of note, however, the 3.8% incidence of esophageal candidiasis rate in the topical corticosteroid group was twice that seen in the placebo arm. Adrenal function as assessed by ACTH stimulation testing at baseline and 12 weeks was normal in 88% of the BOS group and 94% of controls.

Bruce Jancin/MDedge News

Dr. Ikuo Hirano

Dr. Hirano noted that adrenal function will continue to be carefully monitored during an ongoing, phase 3, double-blind, placebo-controlled BOS maintenance study.

He reported receiving research funding from and serving as a consultant to Takeda, the study sponsor, as well as a handful of other pharmaceutical companies.

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PERSPECTIVE

New hope for EoE treatment

This is an exciting abstract from Hirano et al. highlighting the results of the first phase 3 trial for an eosinophilic esophagitis (EoE) treatment. Furthermore, the trial design, which included histologic and symptom-based endpoints, may be critical to attaining Food and Drug Administration approval. Given the lack of any FDA-approved therapies for EoE, the results of this trial are welcome news for clinicians who treat patients with EoE.

Dr. Menard-Katcher

This study of a topical muco-adherent steroid formulation (budesonide oral suspension) specifically designed to treat EoE significantly improved histologic, symptom, and endoscopic endpoints, compared with placebo. Of note, 62% of patients on the drug achieved a histologic response of less than 15 eosinophils per high-power field (53% achieved less than 6), compared with 1% in the placebo group. This study supplements the existing data supporting the use of swallowed topical steroids in EoE.

It is important to note that the subjects in this study had fairly severe disease, with more than 40% having previously undergone esophageal dilation and all patients experiencing dysphagia, on average, multiple times per week. Given the disease severity in the subject population, there can be even greater enthusiasm regarding the response rates for the budesonide group. Also notable is the relatively high dose of budesonide used in this study (2 mg twice daily), which may have contributed to the 3.8% incidence of esophageal candidiasis. Importantly, adrenal function was assessed during the study and will be monitored during the ongoing maintenance portion of the study.

These last points do highlight the challenges of treating more severe EoE given 38% of patients did not achieve histologic remission (less than 15 eosinophils per high-power field) despite the doses of budesonide used in this study. This emphasizes the need for other treatment options for steroid nonresponders.

Taken together, these results are very exciting and will lead to an FDA-approved EoE treatment in short order.

Paul Menard-Katcher, MD, is associate professor of medicine in the division of gastroenterology and hepatology at the University of Colorado at Denver, Aurora. He has no conflicts of interest.

Is enforcement restriction needed?

Transplants *from page 1*

since 2013 – in which the FDA has exercised "enforcement discretion," should be allowed to continue.

"Enforcement discretion has been successful in enabling and overcoming key barriers to access to treatment," said Majdi Osman, MD, clinical program director at OpenBiome, a nonprofit stool bank based in Cambridge, Mass. Dr. Osman said that 98% of the U.S. population now lives within a 2-hour drive of an FMT provider.

Amanda Kabage, a researcher and donor program coordinator for the Microbiota Therapeutics program at the University of Minnesota in Minneapolis, and herself a former recipient of FMT, said she was in favor of continuing the FDA policy.

"If enforcement discretion were to go away, patients far sicker than I was will not have access. They'll get sicker and they will die," Ms. Kabage said.

But, she added, the FDA had missed an opportunity by not insisting on collecting outcomes and safety data. Minnesota has established a patient registry to do just that, and physicians cannot administer FMT unless they agree to participate, she said. In response, FDA panelists noted that the agency cannot mandate data collection under an enforcement policy.

Lee Jones, founder and chief executive officer of Rebiotix/Ferring, a biotech company focused on the development of microbiome-based therapeutics, argued for tighter restrictions, however, claiming that increased access – and the FDA policy – had led to a fourfold decrease in enrollment since the company began study of its lead FMT product, RBX2660, in 2013.

"We're dealing with an orphan indication and the patients were hard to come by to begin with," she said at the meeting. "Enforcement discretion has slowed our clinical development and delayed patient access to FDA-approved therapies by over 2 years."

An investigator at the University of Texas Health Science Center at Houston, Herbert DuPont, MD, who has administered FMT and is conducting a trial for Rebiotix, said his center wanted the FDA policy to continue "allowing multiple groups to perform FMT for recurrent [*Clostridium difficile*], because of the incredible public health need."

But, he added, "We're very concerned about industry and ability to do clinical trials."

Those trials are important, Dr. DuPont said. "I think we have to address very actively how industry can move these products through," he said, "because all of us want to remove the F from FMT," by isolating the necessary elements of the process while not having the risk sometimes associated with human stool.

Policy slow to evolve

"I'm frustrated that it's taken over 6 years and three draft guidances to get us this far," Christian John Lillis, executive director of the Peggy Lillis Foundation – a group dedicated to creating awareness about the dangers of *C. difficile* – said at the meeting.

Mr. Lillis said that probably several thousand deaths had been prevented

Continued on following page

A sepsis death linked to fecal microbiota transplantation

BY BIANCA NOGRADY
MDedge News

Two cases of bacteremia have been described in two patients who received fecal microbiota transplants from the same donor.

Writing in the New England Journal of Medicine, researchers reported the two case studies of extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* bacteremia, one of which ended in the death of the patient. These cases were previously announced by the FDA in a June 2019 safety alert.

Zachariah DeFilipp, MD, from Massachusetts General Hospital at Harvard Medical School, Boston, and coauthors wrote that fecal microbiota transplantation (FMT) is rarely associated with complications. Placebo-controlled trials and a systematic review have found similar rates of complications in immunocompromised and immunocompetent recipients. Only four cases of gram-negative bacteremia have previously been reported, and in three of these, there was a plausible alternative explanation for the bacteremia.

In this paper, both patients received fecal microbiota transplantation via frozen oral capsules containing donor stool. These capsules were prepared prior to the implementation of screening for ESBL-producing organisms at the instutions, and were not retrospectively tested since this expanded donor screening.

The first patient was a 69-year-old man with liver cirrhosis attributed to hepatitis C infection who was enrolled in a trial of fecal microbiota transplantation via oral capsules to treat hepatic encephalopathy.

The first sign of the adverse event was a fever and cough, which developed 17 days after the final dose of 15 capsules. He was treated for pneumonia but failed to improve after 2 days, at which time gram-negative rods were discovered in blood cultures taken at the initial presentation.

After admission and further treatment, blood cultures were found to have ESBL-producing *E. coli*, and after further treatment, the patient was clinically stable. A stool sample taken after treatment was negative for ESBL-producing *E. coli*.

The second case study was a 73-year-old man with therapy-related myelodysplastic syndrome who was undergoing allogeneic hematopoietic stem cell transplantation and was receiving fecal microbiota transplantation via oral capsules as part of a phase 2 trial.

Eight days after the last dose of oral capsules, and 5 days after the stem cell infusion, the man developed a fever, chills, and febrile neutropenia and showed altered mental status. He was treated with cefepime but developed hypoxia and labored breathing later that evening, which prompted clinicians to intubate and begin mechanical ventilation.

His blood culture results showed gram-negative rods, and meropenem was added to his antibiotic regimen. However, the patient's condition worsened, and he died of severe sepsis 2 days later with blood cultures confirmed as positive for ESBL-producing *E. coli*.

A follow-up investigation revealed that both patients received stool from the same donor. Each lot of three capsules from that donor was found to contain ESBL-producing *E. coli* with a resistance pattern similar to that seen in the two recipients.

Twenty-two patients had received capsules from this donor. Researchers contacted all the recipients and offered them stool screening for ESBL-producing *E. coli*. Twelve underwent testing, which found that five had samples that grew on ESBL-producing *E. coli*–selective medium.

The remaining seven patients who had follow-up testing were receiving treatment for recurrent or refractory *Clostridioides difficile* infection, and four of these grew samples on the selective medium.

"When FMT is successful, the recipient's metagenomic burden of antimicrobial resistance genes mimics that of the donor," the authors wrote. "Although we cannot conclusively attribute positive screening results for ESBL-producing organisms

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PERSPECTIVE

Balance risks and benefits of FMT

Fecal microbiota transplantation could have therapeutic utility in a range of conditions in which primary dysbiosis is suspected, but this study shows the procedure may carry risks that become apparent only after treatment. Improved screening of donors and fecal material could reduce the risks of infections by known agents. However, new pathogens may not be recognized until after they have been transplanted into a new host.

The benefits and risks of fecal microbiota transplantation must be balanced, but up to now the complications have been infrequent and the benefits have clearly outweighed the risks.

Martin J. Blaser, MD, is from Rutgers University in New Brunswick, N.J. These comments are adapted from an accompanying editorial (N Engl J Med. 2019 Oct 30. doi: 10.1056/NEJMe1913807). Dr. Blaser declared personal fees and stock options from the medical sector unrelated to the work.

Continued from previous page

through increased FMT access, but that it was time to create a concrete policy that advanced the therapy.

The FDA guidance issued in 2013 allowed physicians to provide FMT for recurrent or refractory *C. difficile* infection without filing an investigational new drug (IND) application.

Clinicians must obtain informed consent that includes a discussion of the risks, and a statement that FMT is investigational. In March 2016, the agency issued a revised draft guidance that it was aiming to require stool banks to apply for INDs, as reported by *Medscape Medical News*.

OpenBiome has flourished under the current policy. It has provided more than 50,000 treatments to 1,200 hospitals and clinics, and has provided FMT for 49 clinical trials and for 16 single patients who received INDs, Dr. Osman said.

But requiring INDs for all centers is a bad idea, he said. "IND requirements are insurmountable for most health centers," Dr. Osman said, noting that most of the FMT material OpenBiome produces is sent to community-based physicians.

"These requirements would likely mean restrictions in access for stool bank–provided FMT and potentially pushing patients to physician-directed FMT or discouraging physicians from using FMT at all," he said.

Stacy Kahn, MD, FMT director at Boston Children's Hospital, said that having ready access from a stool bank was crucial.

"Universal donor FMT is much easier, much faster, and much more cost effective than what we can do as clinicians," she said.

Safety, efficacy data emerge

One unpublished study showed that 75% of patients treated since 2011 had a sustained cure, noted Colleen Kelly, MD, a Brown University professor of medicine and principal investigator for the National Institutes of Health–funded national FMT registry (although the data in the study were not from the national FMT registry).

The study, which was a collaboration between the Alpert Medical School of Brown University, Brigham and Women's Hospital, and Indiana University School of Medicine, attempted follow-up on 533 patients; 208 were successfully contacted, and an additional 55 had died, none due to FMT.

Dr. Kelly presented data from the FMT National Registry showing that, at 1 month post transplant, 2 (1%) of 253 patients had an infection possibly related to FMT; 1 with *Bacteroides fragilis* and 1 with enteropathogenic *E. coli*. Seven hospitalizations were deemed related or possibly related to FMT, including two recurrences of *C. difficile*.

At 6 months post transplant, 8 (5%) of 152 patients had a serious infection, and 23 patients reported a diagnosis of a new condition, primarily diarrhea-predominant irritable bowel syndrome, which is common post FMT, said Dr. Kelly, who presented the data on behalf of AGA, which administers the registry.

The AGA supports a continuation of the enforcement discretion as a means to maintain patient access where the evidence supports the use of FMT, but the group does not back use of FMT outside medical supervision, Dr. Kelly said.

This article originally appeared on Medscape.com.

Patients and physicians may like it

Telemedicine *from page 1*

people think of when they imagine telemedicine, she said.

There's increasing acceptance of telehealth services, said Dr. Lee, with a recent online poll showing that two-thirds of those surveyed would be willing to use telehealth; this would translate to about 24 million Americans who would be potential telehealth patients. And a 2019 survey of internal medicine physicians showed that more than half are working in practices in which telehealth is used in some capacity. Both patients and clinicians can benefit in a telehealth relationship, said Dr. Lee. The lack of physical travel and the potential for access after normal clinic hours can be a real boon for patients; "So how does this help us? How does it improve practice and make our lives easier?" she asked. Telehealth services can lead to improved efficiency, patient satisfaction and retention, and the ability to stand out in a market, especially if a practice can initiate telehealth services now, during the rapid growth and adoption phase for this newer technology.

"You want to make sure you really understand what some of the legal issues are surrounding telehealth and telemedicine," said Dr. Lee, to ensure compliance with state and federal laws. There can be barriers to practicing across state lines; some states require an initial in-person visit, or the signing of a consent form, before initiating telemedicine; others may limit controlled substance prescribing via telemedicine.

And the mode of communication matters, said Dr. Lee: "Why can't we just use Facetime to call our patients? The first thing to think about is privacy, and unauthorized access to data," so it's critical to do your research and use fully HIPAA-compliant communications technology.

Technology – and pricing plans – can vary widely, she added. "There's some benefit to including technology that integrates with other clinical programs"; the platform Dr. Lee's group chose communicates with their EHR for such functions as scheduling.

Pricing models can vary; a common scheme charges a per-user monthly fee, though blanket-fee plans also exist. Some telemedicine platforms use a hybrid pricing model that charges a flat fee up to a certain number of users and then adds a per-user fee after that.

Best practices to manage liability include continuing to maintain high standards of compliance after attorney consultation and notifying your practice's malpractice insurance carrier, said Dr. Lee.

Reimbursement is on the upswing, as insurers see the benefits of telemedicine, and employers see their patients needing less time off work for appointments, and there are fewer emergency department visits for after-hours problems. Medicaid reimbursement is fairly straightforward, but Medicare is more restrictive and requires the beneficiary to be in a rural originating site.

Coding for a telemedicine visit is strictly based on face-to-face time spent in video conference, said Dr. Lee, at levels on par with time-based coding for office visits. "But you're not including that time you spend doing chart review and not including the time you spend coordinating care."

Dr. Lee's own experience with telemedicine began in late 2016, when the 22-physician general gastroenterology group looked into it as a way to increase growth.

During the first half of the next year, the gastroenterology group's administrative leaders and an engaged physician proponent vetted a number of telemedicine companies, and the group tried the leading candidates' technologies.

By mid-2017, the comprehensive gastroenterology group, which also employs six advanced-practice clinicians, was piloting video visits with a group of four physicians. "One of those physicians was actually one of my partners who had

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in other asymptomatic recipients to FMT, the rates of positive tests are, in our opinion, unexpectedly high and probably represent transmission through FMT."

The authors said the donor had no risk factors for carriage of multidrug-resistant organism and had previously donated fecal material before the introduction of routine screening for ESBL-producing organisms.

However, they noted that both patients had risk factors for bacteremia, namely, advanced cirrhosis and allogeneic hematopoietic stem cell transplantation and they also received oral antibiotics around the time of the fecal microbiota transplantation.

"Despite the infectious complications reported here, the benefits of FMT should be balanced with the associated risks when considering treatment options for patients with recurrent or refractory *C. difficile* infection," the authors wrote. "Ongoing assessment of the risks and benefit of FMT research is needed, as are continuing efforts to improve donor screening to limit transmission of microorganisms that could lead to adverse infectious events."

The American Gastroenterological Association FMT National Registry is a critical effort to track short- and long-term patient outcomes and potential risks associated with FMT. The registry's goal is to track 4,000 patients for 10 years. If you perform FMT, please contribute to this important initiative. Learn more at www.gasatro.org/FMTRegistry.

The study was supported by a grant from the American College of Gastroenterology. Three authors declared personal fees and grants from the medical sector outside the submitted work, and two were attached to a diagnostics company involved in the study.

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SOURCE: DeFilipp Z et al. N Engl J Med. 2019 Oct 30. doi: 10.1056/NEJMoa1910437.

sustained an Achilles tendon injury, so wasn't really coming to the office post surgery. He was starting to use this at home, to do video visits, and everything went pretty smoothly with that," said Dr. Lee.

When this trial was successful, the group went all in, with on-boarding of clinicians accomplished by the end of the year, and site visits and 1:1 training provided by the telemedicine platform providers.

The practice is seeing video visits continue to grow in popularity, among both patients and clinicians, said Dr. Lee. She shared some tips and lessons learned from her practice.

Connectivity problems on the patient end are fairly frequent, and no-shows also can be a problem. On the clinic side, not all clinicians have embraced video visits.

There's currently no formal protocol that selects patients for participation in the telemedicine program at Dr. Lee's clinic. Providers may offer video visits to patients, and triage nurses also can suggest that patients ask their provider about them; flyers in waiting rooms and exam rooms encourage patients to ask about the possibility.

The practice maintains a telehealth committee that includes the practice's president and administrator, about three core physicians who are strong telehealth champions, and additional physicians who are high telehealth users. The committee also folds in the office and information technology managers to make sure issues of workflow, billing, and technology are addressed.

Some practical considerations can pose challenges to a successful telemedicine program, said Dr. Lee. Connectivity problems on the patient end are fairly frequent, and no-shows also can be a problem. On the clinic side, not all clinicians have embraced video visits. For these low users, telemedicine may not represent a good value proposition. However, she said, they are seeing more and more clinicians come on board with video visits as word gets out of the generally positive experiences others are having.

Dr. Lee suggested several ways to up telemedicine utilization and make it work within your practice. "Identify which patient would benefit most," she said – this might be patients with inflammatory bowel disease who mostly need medication management, or patients with limited mobility or who live far away. Staff can also help a patient get a same-day visit by scheduling a video visit with an available clinician. By mentioning video visits as an option for uncomplicated issues or a way to get a rapid read on a new concern, clinicians can get patients thinking about telemedicine as an appealing option.

In some clinics, exam room space can limit clinician productivity, and scheduling a block of video visits when space is tight can be a great solution. Clinicians can optimize their schedules if they incorporate video visits, said Dr. Lee, citing the example of a physician assistant in her practice who stacks video visits in the evening hours, so she's able to be with her preschool-aged children during the day. After-hours video visits have been popular among patients too, said Dr. Lee, so the scheduling flexibility may help with both patient and provider retention, and be a practice differentiator.

"There's great potential for value through improved patient satisfaction, provider efficiency, improved health care outcomes, and cost efficiency," she said.

Dr. Lee reported that she had no relevant disclosures.

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➤ PRACTICE MANAGEMENT TOOLBOX:

Burnout – what is it, why we're talking about it, and what does it have to do with you?

BY JOANNA LAW, MD

There has been a great deal of evolving research and writing about physician burnout. Horror stories about long work hours, frustrations with working environments, administrative challenges are everywhere – social media, medical journals, mainstream media. While burnout is not new, the increased attention and consequences in the health care system are exposing not only the importance of physician well-being but also the impact of burnout on patient care.

What is burnout?

Burnout was first identified in the 1970s and further refined by Christina Maslach, PhD, as a syndrome that is due to prolonged exposure to chronic interpersonal stress with three key dimensions that include 1) overwhelming exhaustion, 2) feelings of cynicism and detachment from the job, and 3) a sense of ineffectiveness and lack of accomplishment.

The Maslach Burnout Inventory (MBI), a 22-item questionnaire that was developed in the 1980s has become the standard survey in research settings for the identification of burnout. However, a two-item questionnaire has been utilized with good correlation to the domains of emotional exhaustion and depersonalization and includes: 1) I feel burned out from my work and 2) I have become more callous toward people since I took this job. Responses are graded on a scale from never to everyday with five points in between; the likelihood of burnout is high when responses are once a week or more frequent (i.e., a few times a week or everyday).

Why are we talking about burnout?

Burnout has far-reaching consequences. It affects not only the individual but also that person's interpersonal relationships with family and friends. Additionally, burnout affects patient care and the overall health care system.

Let's imagine the scenario in which you arrive at your office on a Monday morning and open your electronic health record. You tend to arrive

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DDSEP 9

Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Correct answer: C

Rationale

There are many potential reasons for PPI failure in patients with symptoms of gastroesophageal reflux. However, the single most important reason is inappropriate drug administration. Patients should be counseled to take their medication 30-60 minutes prior to meals for optimal physiologic gastric acid inhibition, with the morning meal favored over the evening meal because of relatively more gastric acid production at this time.

Reference

Fass R, Shapiro M, Dekel R. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease – where next? Aliment Pharmacol Ther. 2005;22:79-94.

Q2. Correct answer: D

Rationale

Elbasvir and grazoprevir are hepaticaly metabolized and undergo minimal renal elimination, making them safe for use in patients with end-stage renal disease. The C-Surfer trial evaluated elbasvir and grazoprevir in genotype 1 patients with advanced renal disease inclusive of patients on hemodialysis. Cure rates in this trial were 94%-99%. Sofosbuvir-containing regimens are not approved for patient with CKD stage 4-5 or those on hemodialysis, even when given in a dose reduced or postdialysis fashion.

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1. https://www.hcvguidelines.org/unique-populations/renal-impairment
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➤ PRACTICE MANAGEMENT

Could the biosimilar market stall before it ever really started?

BY GREGORY TWACHTMAN
MDedge News

NATIONAL HARBOR, MD. – If the United States does not step up and create a thriving biosimilars market soon, it risks destroying the market not only domestically but internationally as well.

This was the warning Gillian Woollett, senior vice president at Avalere, provided to attendees at the annual meeting of the Academy of Managed Care Pharmacy.

She prefaced her warning by quoting Alex M. Azar III, secretary of Health & Human Services, who said that those "trying to hold back biosimilars are simply on the wrong side of history," though Ms. Woollett said they "may be on the right side of the current economic model in the United States."

And despite the probusiness, procompetition philosophy of current HHS leadership, there has been very little movement on creating a competitive market for biosimilars in the United States, evidenced by the very expensive regulatory requirements that biosimilar manufacturers need to meet in order to get products to market.

Gregory Twachtman/MDedge News

Gillian Woollett

"It's not that we won't have competition in the U.S.," she said. "I think we will. We do have that innovation. ... It's just that biosimilars may not ultimately be part of that competition. And for that, we will pay a price, and I actually think the whole world will pay a price because if we are not providing the [return on investment], I am not sure the other markets can sustain it."

One issue biosimilars have is the lack of recognition of the value that they bring.

"That biosimilars offer the same clinical outcomes at a lower price is yet to be a recognized value," she said. "To me that's a really surprising situation in the United States."

Ms. Woollett disclosed no relevant conflicts of interest.

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AGA Resource

To prepare for the entry of biosimilars to the market, AGA is taking the lead in educating health care providers and patients about biosimilars and how they can be used for IBD patient care. Learn more at www.gastro.org/biosimilars.

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at work about 45 minutes prior to your first patient to try to catch up with messages. As you wait for your computer to log in (5 minutes? 8 minutes? 12 minutes?) and Citrix to connect, you are eating your breakfast bar and drinking mediocre coffee because you still haven't had time to fix your coffee machine at home (should you just order a new one on Amazon and contribute to the world's growing trash problem?).

Once you log in to your EHR, the first three messages are about missing charges and charts still left open – yes, you haven't corrected the resident's note from clinic on Friday afternoon, yet.

The next two messages are about insurance denials for a prescription or a procedure or an imaging study. You decide that perhaps you should change gears and check your work email. The first email is a reminder that vacation requests for the next 6 months are due by end of business today and any requests made after today must go through some administrative approval process that seems inefficient and almost punitive (mainly because you forgot to discuss this with your partner and family and you are feeling somewhat guilty but resentful of this arbitrary deadline that was announced last week).

Your pager promptly buzzes to announce that the first patient has arrived and is ready for you to consult. As you walk over to the procedure area, you remind yourself to finalize the resident's note from Friday, file the missing charges, close those charts, and find some reasonable evidence to justify the medication/test/procedure so that your patient is not saddled with a large bill. And as you walk up to your first patient of the morning, you are greeted by a nurse who indicates the patient doesn't have a ride home post procedure and what do you want to do?

Does any of this sound remotely familiar? In today's medical practice, there are multiple factors that contribute toward burnout, including excessive clerical burden, inefficient EHR and computer systems, and the sense of loss of control and flexibility, along with problems associated with work-life balance.

What does it have to do with you?

According to two surveys administered by the AGA and ACG, burnout occurs in approximately 50% of gastroenterologists. It also appears that burnout starts as early as the fellowship years when there is even less control, long work hours, and similar demands with regards to work-life balance.

Burnout is prevalent among gastroenterologists, and it can start early. There is evidence to suggest that procedure-based specialties are at higher risk because of the added possibility of complications associated with procedures. It is important for us to recognize signs of burnout not only in ourselves but also in our colleagues and understand what personal and system-related triggers and solutions are present. The consequences of burnout have been reported to include earlier retirement and/or career transitions and are associated with depression, the risk of motor

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vehicle accidents, substance abuse, and suicide.

At the systems level, changes can be made to mitigate known pressures that contribute to burnout. There are efforts such as improved workflow and specific quality improvement initiatives that can improve physician satisfaction. Ensuring adequate support for physicians with aids such as scribes and appropriate support staff and para–health care workers can significantly decrease the administrative burden on clinicians and improve productivity and patient care.

At a broader level, talking about burnout, recognizing the signs of burnout, and also ensuring the appropriate support is available for physicians who are at risk or already experiencing burnout can arise from leadership at both the institutional level but also at the larger organizational level, where there is greater investment into the health and well-being of physicians. For example, societies can have the negotiating power to advocate to simplify tasks unique to gastroenterologists with regard to reimbursement or EHR pathways. Academic centers can incorporate classes and forums for medical students, trainees, and practicing physicians that focus on health and well-being.

Ultimately, we are all in this together – burnout affects all of us no matter what hat you want to wear – provider, colleague, patient, or friend.

At the individual level, we should be able to reach out to our colleagues to ask for help or to see if they need help. We also need to better identify what our triggers are and what are remedies for these triggers. It's not normal to be in a profession in which you have a constant sensation that you are drowning or barely treading water but I am sure many of us have felt this at some point if not with some regularity. So as a practitioner, what coping mechanisms do you have in place? There has been some work with respect to adaptive and maladaptive coping mechanisms at the individual and organizational levels. Maladaptive mechanisms can result in significant personal health issues including hypertension, substance abuse, and depression; it can also further exacerbate burnout symptoms in the provider and result in patient-related complications, shortened provider career trajectories, and increased strains on provider's interpersonal relationships. I think it is an important point here to make that there are likely sex differences in maladaptive coping mechanisms and manifestations of burnout with work that suggests that women are more prone to depression, isolation, and suicide compared with male colleagues.

With respect to adaptive coping mechanisms, the most common theme is to not isolate yourself or others. Ask a colleague how s/he is doing – we are all equally busy but sometimes just popping into someone's office to say hello is enough to help another person (and yourself) connect. Additionally, it's not too much to ask for professional help. What we do is high stakes and taking care of ourselves usually comes behind the patient and our families. But who takes care of the caregiver? Working on interpersonal relationships can strengthen your resilience and coping techniques to the stressors we face on a daily basis. Ultimately, we are all in this together – burnout affects all of us no matter what hat you want to wear – provider, colleague, patient, or friend.

Dr. Law is a gastroenterologist at the Virginia Mason Medical Center in Seattle. She has no conflicts of interest.

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PROFESSIONAL OPPORTUNITIES

Bariatric surgery shows metabolic benefits in patients with BMI less than 35 kg/m^2

BY MITCHEL L. ZOLER
MDedge News

LAS VEGAS – It's time to take bariatric out of bariatric surgery.

"The way forward is to not call it bariatric surgery or weight-loss surgery but surgery to treat diabetes, hypertension, hyperlipidemia, and other metabolic diseases," said Oliver A. Varban, MD, at a meeting presented by the Obesity Society and the American Society for Metabolic and Bariatric Surgery. "We need to reframe the conversation with patients about what success [with bariatric surgery] looks like. Weight loss can be a side effect of the operation if patients have surgery to resolve their diabetes. It's not about BMI; it's about treating metabolic disease."

Dr. Varban, a bariatric surgeon at the University of Michigan in Ann Arbor, reported data showing that bariatric surgery with sleeve gastrectomy in patients with baseline body mass index levels below 35 kg/m^2 was as effective at normalizing a range of metabolically associated disorders as it was in more obese patients in an observational study of more than 45,000 patients who underwent surgery in Michigan.

The findings add to an already extensive pool of evidence for loosening current guidelines that restrict bariatric surgery to patients with a BMI of 35 kg/m^2 or greater, Dr. Varban said. But an influential bariatric surgery consensus statement from the National Institutes of Health that dates from 1991 and remains in place, recommends this surgery only for people with a BMI of at least 35 kg/m^2, and this guidance often limits access to the surgery for patients at lower BMI, he noted.

A more inclusive assessment of patients as potential candidates for bariatric surgery should include a range of considerations in addition to weight and height, he explained in an interview. "Even if people have a BMI of less than 30 kg/m^2 but have, or are at high risk for developing, metabolic disease, they should also be offered the operation."

The guidance from the NIH results in a U.S. bariatric surgery population that effectively centers mainly on women with a BMI of 40 kg/m^2 or greater and makes procedures like sleeve gastrectomy unavailable to many other types of patients who could benefit from it, Dr. Varban said. In 2018, the American Society for Metabolic and Bariatric Surgery released a position statement that summarized the evidence for the safety and efficacy of bariatric surgery in people with a BMI of 30-34 kg/m^2, and cited the lingering and restrictive impact of the 1991 NIH consensus statement.

The study run by Dr. Varban and his associates used data collected by 43 programs in the Michigan Bariatric Surgery Collaborative during 2006-2018 that included 1,073 patients who had a BMI of less than 35 kg/m^2 on the day they underwent sleeve gastrectomy, and 44,511 patients who had the same procedure and had a BMI of at least 35 kg/m^2.

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The operations were performed by any 1 of 81 surgeons who worked at the centers during this time.

The patients with lower BMIs were older, with an average age of 51 years, compared with 45 years in the higher-BMI group, and they had higher prevalences of certain metabolic disorders. Diabetes affected 37% of those in the lower-BMI group and 31% of those with higher BMIs; hyperlipidemia affected 57% and 45%, respectively; and gastroesophageal reflux disease affected 56% and 49%, respectively. Obstructive sleep apnea was more common in the group with higher BMIs, at 47%, compared with 41% of those with lower BMIs.

The average BMI in the lower group was 33.7 kg/m^2; in the higher group it was 46.7 kg/m^2. Dr. Varban did not have data on whether any patients in the lower-BMI group had a BMI below 30 kg/m^2. Roughly a third of the patients in the lower-BMI group had a BMI of less than 35 kg/m^2 at the time of their initial examination, whereas the other two-thirds had a BMI that low only on the day of their surgery.

At follow-up 1 year after their surgery, patients who started with lower BMIs had, in general, a very similar pattern of responses as those who started with higher BMIs, with rates of discontinuation of treatments for diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, and gastroesophageal reflux of about 50%-80% and similar in both treatment arms. For example, discontinuation of oral diabetes drugs occurred in 79% and 78% of those with low and high BMIs, respectively, and discontinuation of hyperten-

PERSPECTIVE

Findings add to a growing evidence base

This is a very important topic and study, and its findings are very positive and reinforcing for more liberal use of bariatric surgery. Results from several prior studies had documented the safety and efficacy of bariatric surgery in patients with lower body mass index, and its fantastic to now have additional data that show the same outcomes. A major challenge is making patients and more physicians aware of the range of comorbidities that can be effectively managed with bariatric surgery, even in patients with lower body mass index.

Mona Misra, MD, is associate director of the Bariatric Program at Cedars-Sinai Marina Del Rey Hospital in Los Angeles. She had no relevant disclosures. She made these comments as designated discussant for the study.

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sion medications occurred in 60% and 54%, respectively. Although the average absolute weight loss in the patients with lower BMIs was nearly half that of patients with higher starting BMIs, a much greater percentage of patients in the lower-BMI group achieved a BMI of less than 25 kg/m^2, compared with the higher-BMI group (36% vs. 6%, respectively).

Patients from the lower-BMI group also showed high levels of satisfaction with their surgery and its results after 1 year. Questionnaire results from roughly half the patients in each treatment group showed that 90% were very satisfied in the lower-BMI group, compared with 84% of those who began with higher BMIs, with a dissatisfaction rate of 1% and 2%, respectively. The average body-image score at 1 year follow-up was significantly higher in those who started with lower BMIs. The rate of complications was low and similar in the two groups, with a 6% rate in the lower-BMI group and 5% in those with higher BMIs.

The study received no commercial funding. Dr. Varban receives salary support from Blue Cross Blue Shield of Michigan.

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SOURCE: Varban OA et al. Obesity Week 2019, Abstract A105.

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