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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

COURTESY DR. JAMI KINNUCAN

Dr. Jami Kinnucan and the AGA workgroup focused on gaps in IBD care related to inflammatory issues, mental health, and nutrition.

AGA introduces pathway to navigate IBD care

BY HEIDI SPLETE
MDedge News

Inflammatory bowel disease (IBD) treatment remains a challenge in part because care is often fragmented among providers in different specialties, according to the American Gastroenterological Association. To address the need for provider coordination, the AGA has issued a new referral pathway for IBD care, published in Gastroenterology.

"The goal of this pathway is to offer guidance to primary care, emergency department, and gastroenterology providers, by helping identify patients at risk of or diagnosed with IBD and provide direction on initiating appropriate patient referrals," wrote lead author Jami Kinnucan, MD, of the University of Michigan, Ann Arbor, and members of the AGA workgroup.

In particular, the pathway focuses on gaps in IBD care related to inflammatory issues, mental health, and nutrition. The work group included not only gastroenterologists, but also a primary care physician, mental/behavioral health specialist, registered dietitian/nutritionist, critical care specialist, nurse practitioner, physician group representa-

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Cost of physician burnout estimated at $4.6 billion a year

BY RICHARD FRANKI
MDedge News

Physician burnout costs the U.S. health care system approximately $4.6 billion a year in physician turnover and reduced productivity, according to the results of a cost-consequence analysis.

In 2015, the burnout-attributable cost per physician was $7,600 – an estimate occupying the conservative middle ground between the $3,700 and $11,000 extremes produced by the study's mathematical model.

"Traditionally, the case for ameliorating physician burnout has been made primarily on ethical grounds." This study, believed to be the first to look at the system-wide costs of burnout, "provides tools to evaluate the economic dimension of this problem," wrote Shasha Han, MS, of the National University of Singapore and her associates in Annals of Internal Medicine.

Individual burnout-attributable costs were higher for physicians in the younger age group (less than 55 years) in all three specialty categories: $7,100 versus $5,900 for those aged at least 55 years among primary care physicians, $10,800 versus $9,100 for surgical specialists, and $7,800 versus $6,100 for other specialists, the investigators reported.

The mathematical model used in the study focused

See **Burnout** · *page 28*

FDA warns about fecal microbiota for transplantation

BY DOUG BRUNK
MDedge News

Officials at the Food and Drug Administration have issued a safety alert regarding the use of fecal microbiota for transplantation (FMT) and the risk of serious adverse reactions because of transmission of multidrug-resistant organisms (MDROs).

According to the alert, which was issued on June 13, 2019, the agency became aware of two immunocompromised adult patients who received investigational FMT and

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News from DDW2019 Digestive Disease Week® in this issue

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LETTER FROM THE EDITOR: Wellness seminars won't fix burnout


DR. ALLEN

"Burnout" has been defined as long-term, unresolvable job stress that leads to exhaustion, depression, and in some tragic circumstances, suicide. One of our lead articles this month concerns an attempt to place a financial cost on physician burnout. More important, I think, is the toll burnout takes on an individual, their family, and their patients. In my role as Chief Clinical Officer of the University of Michigan Medical Group (our faculty and other clinical providers), I struggle to balance productivity demands with the increasing damage such demands are doing to our clinicians. Few primary care physicians at Michigan Medicine work as full-time clinicians (defined as 32 hours patient-facing time per week for 46 weeks). Almost all request part-time status if they do not have protected, grant-funded time. They simply cannot keep up with the documentation required in our electronic health record, combined with our "patient-friendly" access via the electronic portal. One-third of the private practice group I helped build was part-time when I left in 2012, and it is not unusual to hear complaints about burnout from my ex-partners.

Let's be clear, burnout is not going to be solved by increasing the resilience of our physicians or sending us to wellness seminars. That approach is a direct blame-the-victim paradigm. Physicians are burned out because of the constant assault on the core reasons we entered medicine – to help people (this assault has been termed "moral injury"). BPAs (best practice alerts), coding requirements, inbox demands, prior authorizations (see the practice management section of this issue), electronic-order entry, and most other practice enhancement tools rely on the willingness of physicians to sacrifice more time and energy and sit in front of a computer screen.

Salvation of our health care system will not come from mass retirements (although that is happening), concierge practices, part-time status, or other individual responses to this crisis. We will need a fundamental reorganization of our practice, where we (physicians) reduce our work to activities for which we trained combined with a shift of nonphysician work to others, better technology, virtual visits, and ancillary personnel. Patient expectations must be realistic and legal protections need strengthening. The politics of health care has focused on funds flow and ideology. We need a stronger voice that articulates the daily microaggressions that we each endure as we try to live Oslerian physician ideals.

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

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz

Q1: A 70-year-old male presents with progressive dysphagia over the past 4 months and 30-pound weight loss. A barium swallow demonstrates a dilated esophagus with a bird's beak appearance.

What is the next best step?
A. Referral for per-oral endoscopic myotomy
B. High-resolution esophageal manometry
C. Calcium channel blocker
D. EGD
E. Placement of G tube

Q2: A 63-year-old woman is admitted with abdominal pain and iron deficiency anemia. She reports long-standing anemia and a negative work-up in the past year including an upper endoscopy, colonoscopy, and video capsule endoscopy. She was started on iron infusions with a modest improvement in her anemia. Her other medical history includes osteoporosis; osteoarthritis, for which she takes over-the-counter NSAIDs, breast cancer (20 years ago treated with lumpectomy and local radiation); and migraines for which she takes sumatriptan once or twice a month.

Which medication puts her at the highest risk for peptic ulcer disease?
A. Iron
B. Sumatriptan
C. Alendronate
D. Tamoxifen

The answers are on page 26.

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FROM THE AGA JOURNALS

Atypical food allergies common in IBS

BY AMY KARON
MDedge News

Among patients with irritable bowel syndrome (IBS) who tested negative for classic food allergies, confocal laser endomicroscopy showed that 70% had an immediate disruption of the intestinal barrier in response to at least one food challenge, with accompanying changes in epithelial tight junction proteins and eosinophils.

Among 108 patients who completed the study, 61% showed this atypical allergic response to wheat, wrote Annette Fritscher-Ravens, MD, PhD, of University Hospital Schleswig-Holstein in Kiel, Germany, and her associates. Strikingly, almost 70% of patients with atypical food allergies to wheat, yeast, milk, soy, or egg white who eliminated these foods from their diets showed at least an 80% improvement in IBS symptoms after 3 months. These findings were published in Gastroenterology.

Confocal laser endomicroscopy (CLE) "permits real-time detection and quantification of changes in intestinal tissues and cells, including increases in intraepithelial lymphocytes and fluid extravasation through epithelial leaks," the investigators wrote. This approach helps clinicians objectively detect and measure gastrointestinal pathology in response to specific foods, potentially freeing IBS patients from highly restrictive diets that ease symptoms but are hard to follow, and are not meant for long-term use.

For the study, the researchers enrolled patients meeting Rome III IBS criteria who tested negative for common food antigens on immunoglobulin E serology and skin tests. During endoscopy, each patient underwent sequential duodenal challenges with 20-mL suspensions of wheat, yeast, milk, soy, and egg white, followed by CLE with biopsy.

Among 108 patients who finished the study, 76 (70%) were CLE positive. They and their first-degree relatives were significantly more likely to have atopic disorders than were CLE-negative patients ($P = .001$). The most common allergen was wheat (61% of patients), followed by yeast (20%), milk (9%), soy (7%), and egg white (4%). Also, nine patients reacted to two of the tested food antigens.

Compared with CLE-negative patients or controls, CLE-positive patients also had significantly more intraepithelial lymphocytes ($P = .001$) and postchallenge expression of claudin-2 ($P = .023$), which contributes to tight junction permeability and is known to be upregulated in intestinal barrier dysfunction, IBS, and inflammatory bowel disease. Conversely, levels of the tight junction protein occludin were significantly lower in duodenal biopsies from CLE-positive patients versus controls ($P = .022$). "Levels of mRNAs encoding inflammatory cytokines were unchanged in duodenal tissues after CLE challenge, but eosinophil degranulation increased," the researchers wrote.

In a double-blind, randomized, crossover study, patients then excluded from their diet the antigen to which they had tested positive or consumed a sham (placebo) diet that excluded only some foods containing the antigen, with a 2-week washout period in between. The CLE-positive patients showed a 70% average improvement in Francis IBS severity score after 3 months of the intervention diet and a 76% improvement at 6 months. Strikingly, 68% of CLE-positive patients showed at least an 80% improvement in symptoms, while only 4% did not respond at all.

"Since we do not observe a histological mast cell/basophil increase or activation, and [we] do not find increased mast cell mediators (tryptase) in the duodenal fluid after positive challenge, we assume a nonclassical or atypical food allergy as cause of the mucosal reaction observed by CLE," the researchers wrote. Other immune cell parameters remained unchanged, but additional studies are needed to see if these changes are truly absent or occur later after challenge. The researchers are conducting murine studies of eosinophilic food allergy to shed more light on these nonclassical food allergies.

Funders included the Rashid Hussein Charity Trust, the German Research Foundation, and the Leibniz Foundation. The researchers reported having no conflicts of interest.

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SOURCE: Fritscher-Ravens A et al. Gastroenterology. 2019 May 14. doi: 10.1053/j.gastro.2019.03.046.

Endoscopist personality linked to adenoma detection rate

BY AMY KARON
MDedge News

Endoscopists who described themselves as "compulsive" and "thorough" had significantly higher rates of adenoma detection, according to results from a self-reported survey of 117 physician endoscopists.

Financial incentives, malpractice concerns, and perceptions of adenoma detection rate as a quality metric were not associated with endoscopists' detection rates in the survey.

"Adenoma detection rates were higher among physicians who described themselves as more compulsive or thorough, and among those who reported feeling rushed or having difficulty accomplishing goals," Ghideon Ezaz, MD, of Beth Israel Deaconess Medical Center in Boston and associates wrote in Clinical Gastroenterology and Hepatology.

These feelings were related to withdrawal times rather than daily procedure volume. "We hypothesize that performing a meticulous examination is mentally taxing and can cause a physician to feel rushed or perceive that it is difficult to keep pace or accomplish goals," the researchers wrote.

Adenoma detection rates vary widely among physicians – up to threefold in some studies. Researchers have failed to attribute most of this discrepancy to seemingly obvious factors such as the type of specialty training an endoscopist completes. The traditional fee-for-service payment model is likely a culprit since physicians are paid for performing as many colonoscopies as possible rather than for procedural quality. Other potential variables include personality traits and endoscopists' knowledge and views on the importance of adenoma detection rates.

To examine the roles of these factors in adenoma detection rates, Dr. Ezaz and coinvestigators used electronic health records data from four health systems in Boston, Pittsburgh, North Carolina, and Seattle. Detection rates were adjusted to control for differences among patient populations. Next, the researchers surveyed the physicians who performed the endoscopies about their financial motivations, knowledge and perceptions of colonoscopy quality, and personality traits.

Among 117 physicians surveyed, the median risk-adjusted adenoma detection rate was 29.3%, with an interquartile range of 24.1%-35.5%. "We found no significant association between adenoma detection rate and financial incentives, malpractice concerns, or physicians' perceptions of adenoma detection rate as a quality metric," the researchers wrote.

In contrast, endoscopists who described themselves as either much or somewhat more compulsive than their peers had significantly higher median adjusted rates of adenoma detection than did endoscopists who described themselves as about the same or somewhat less compulsive than others. These adenoma detection rates, in respective order, were 33.1%, 32.9%, 26.4%, and 27.3% ($P = .0019$). Adenoma detection rates also were significantly higher among physicians who described themselves as more thorough than their peers, who said they felt rushed during endoscopy, and who reported having difficulty pacing themselves, accomplishing goals, or managing unforeseen situations.

A secondary analysis revealed the same links between personality traits and adenomas per colonoscopy. The findings support an expert's prior assertion (Gastrointest Endosc. 2007 Jan;65[1]:145-50) that the best endoscopists are "slow, careful, and compulsive," the researchers noted. They recommended nurturing "meticulousness and attention to detail" during training and evaluating trainees based on these characteristics.

The National Cancer Institute provided funding. The researchers reported having no conflicts of interest.

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SOURCE: Ezaz G et al. Clin Gastroenterol Hepatol. 2018 Oct 13. doi: 10.1016/j.cgh.2018.10.019.

FROM THE AGA JOURNALS

Tofacitinib upped herpes zoster risk in ulcerative colitis

BY AMY KARON
MDedge News

Among patients with moderate to severe ulcerative colitis (UC), a median of 1.4 years and up to 4.4 years of tofacitinib therapy was safe apart from a dose-related increase in risk of herpes zoster infection, according to an integrated analysis of data from five clinical trials.

Compared with placebo, a 5-mg twice-daily maintenance dose of tofacitinib (Xeljanz) produced a 2.1-fold greater risk of herpes zoster infection (95% confidence interval, 0.4-6.0), while a 10-mg, twice-daily dose produced a statistically significant 6.6-fold increase in incidence (95% CI, 3.2-12.2).

Except for the higher incidence rate of herpes zoster, "in the overall cohort, the safety profile of tofacitinib was generally similar to that of tumor necrosis factor inhibitor therapies," wrote William J. Sandborn, MD, AGAF, director of the inflammatory bowel disease center and professor of medicine, at the University of California, San Diego, and associates. The findings were published in Clinical Gastroenterology and Hepatology.

Tofacitinib is an oral, small-molecular Janus kinase inhibitor approved in the United States for moderate to severe UC, as well as rheumatoid and psoriatic arthritis. The recommended UC dose is 10 mg twice daily for at least 8 weeks (induction therapy) followed by 5 or 10 mg twice daily (maintenance). The safety of tofacitinib has been studied in patients with rheumatoid arthritis through 9 years of treatment. To begin a similar undertaking in UC, Dr. Sandborn and associates pooled data from three 8-week, double-blind, placebo-controlled induction trials, as well as one 52-week, double-blind, placebo-controlled maintenance trial and one ongoing open-label trial. All patients received twice-daily tofacitinib (5 mg or 10 mg) or placebo.

In 1,157 tofacitinib recipients in the pooled analysis, 84% received an average of 10 mg twice daily. For every 100 person-years of tofacitinib exposure, there were an estimated 2.0 serious infections, 1.3 opportunistic infections, 4.1 herpes zoster infections, 1.4 malignancies (including nonmelanoma skin cancer, at an incidence of 0.7), 0.2 major cardiovascular events, and 0.2 gastrointestinal perforations. The likelihood of these events did not increase with time on tofacitinib.

Worsening UC was the most common serious adverse event for patients who received both induction and maintenance therapy. For patients on maintenance therapy, only herpes zoster infection had a higher incidence than placebo, which reached significance at the 10-mg dose. These safety findings resemble those in rheumatoid arthritis trials of tofacitinib, and apart from herpes zoster, they also resemble safety data for vedolizumab (an integrin receptor antagonist), and anti–tumor necrosis factor agents in UC, the researchers wrote.

There were four deaths during the entire tofacitinib UC program, for an incidence rate of 0.2 per 100 person-years of exposure. All occurred in patients receiving 10 mg twice daily. Causes of death were dissecting aortic aneurysm, hepatic angiosarcoma, acute myeloid leukemia, and pulmonary embolism in a patient with cholangiocarcinoma that had metastasized. Concerns about pulmonary embolism have led the European Medicines Agency to recommend against the use of 10-mg twice daily tofacitinib dose in patients at increased risk for pulmonary embolism.

"Compared with prior experience with tofacitinib in rheumatoid arthritis, no new or unexpected safety signals were identified," the researchers concluded. "These safety findings support the long-term use of tofacitinib 5 and 10 mg twice daily in patients with moderately to severely active" UC.

Pfizer makes tofacitinib, funded the individual trials, and paid for medical writing. Dr. Sandborn disclosed grants, personal fees, and nonfinancial support from Pfizer and many other pharmaceutical companies.

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SOURCE: Sandborn WJ et al. Clin Gastroenterol Hepatol. 2018 Nov 23. doi: 10.1016/j.cgh.2018.11.035.

DR. SCHWARTZ

As new mechanisms of action become available for ulcerative colitis (UC) drugs, clinicians must weigh the risks versus benefits. In this article, Sandborn and colleagues provide additional information on the safety profile of tofacitinib. They report an increased risk of herpes zoster that was dose dependent (sixfold increase on 10 mg twice daily). The overall safety profile was reassuring, is similar to the rheumatoid arthritis population treated with tofacitinib, and is in line with the safety profile of anti-TNF antibodies (excluding the increased risk of zoster). With a nonlive zoster vaccine now available, some have advocated vaccinating all patients being started on tofacitinib. However, there is a theoretical risk of disease exacerbation; ongoing studies will hopefully answer this question.

Another emerging safety concern with tofacitinib involves venous thromboembolism (VTE). The Food and Drug Administration recently issued a warning based on the findings of a safety trial in rheumatoid arthritis in which they found an increased risk of PE and death in those on a 10-mg twice-daily dose. The exact details of the risk have yet to be released. Enrollment in the trial required patients aged over 50 years with at least one cardiovascular risk factor. The European regulatory body recently forbade the use of the 10-mg tofacitinib dose for anyone at increased risk for VTE. It is unclear if this risk applies to those younger than 50 years without cardiovascular risk factors or the UC population. In the current study of UC patients, the rate of a major cardiovascular event was rare (n = 4; IR, 0.2). In the short term, it may be prudent to restrict the 10-mg twice-daily dose to those who do not fall into the high-risk category, or try to reduce the dose to 5 mg twice daily if possible.

David A. Schwartz, MD, AGAF, professor of medicine, division of gastroenterology, hepatology and nutrition, Inflammatory Bowel Disease Center, Vanderbilt University, Nashville. He has served as a consultant for Pfizer in the past.

Inducible nitric oxide synthase promotes insulin resistance in obesity

BY AMY KARON
MDedge News

Obesity promotes the localization of inducible nitric oxide synthase (iNOS) in hepatic lysosomes, leading to a cascade of downstream effects that include excess lysosomal NO production, reduced hepatic autophagy, and insulin resistance, investigators reported.

"It is well known that in the context of obesity, chronic inflammation and lysosome dysfunction coexist in the liver," wrote Qingwen Qian, PhD, of the University of Iowa in Iowa City and associates in Cellular and Molecular GI and Hepatology."Our studies suggest that lysosomal iNOS-mediated NO signaling disrupts hepatic lysosomal function, contributing to obesity-associated defective hepatic autophagy and insulin resistance." They noted that the findings could hasten the development of new treatments for metabolic diseases.

Lysosomes recycle autophagocytosed intracellular and extracellular material, which is crucial to maintain several types of homeostasis within the liver; they help regulate nutrient sensing, glycogen metabolism, cholesterol trafficking, and viral defense.

Activation of iNOS is a hallmark of inflammation, and iNOS levels are known to be elevated in the livers of patients with hepatitis C, alcoholic cirrhosis, and alpha 1-anti-trypsin disorder, the researchers wrote. But it was unclear whether NO in hepatocytes was generated by local iNOS or localized to lysosomes.

The researchers therefore studied cell cultures of primary murine hepatocytes by measuring their lysosomal activity, autophagy levels, and NO levels.

They also studied a murine model of diet-induced obesity in which

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60% of calories were from fat. They performed glucose tolerance tests by means of intraperitoneal glucose injections and studied the effects of insulin infusion. Finally, they performed immunohistology, immunohistochemistry, electron microscopy, and measurements of nitrosylated proteins and lysosomal arginine in frozen liver sections from the mice. Lysosomal arginine is required to catalyze NO production in the setting of inflammation as observed in obesity. In fact, concomitant stimulation of lysosomal arginine transport and activation of mTOR (an enzyme which tightly regulates transcription factor EB [TFEB]) was sufficient to stimulate lysosomal NO production in hepatocytes even in the absence of an inflammatory stimulus; pointing to a central role for these processes.

The researchers found that a NO scavenger diminished lysosomal NO production, while overexpression of both mTOR and a lysomal arginine transporter upregulated lysosomal NO production and suppressed autophagy. In mice with diet-induced obesity, deleting iNOS also improved nitrosative stress in hepatic lysosomes, promoted lysosomal biogenesis by activating TFEB, enhanced lysosomal function and autophagy, and improved hepatic insulin sensitivity. Insulin sensitivity diminished, however, when the researchers suppressed TFEB or autophagy-related 7 (Atg7).

Usually, iNOS is primarily expressed in hepatic Kupffer cells, but obesity increases the expression of iNOS in hepatocytes, which promotes hepatic insulin resistance and inflammation, the researchers commented. "Nevertheless, our data showed that liver-specific iNOS suppression has a protective role," they wrote. "We showed that iNOS inactivates [TFEB], and that suppression of [TFEB] and Atg7 diminishes the improved hepatic insulin sensitivity by iNOS deletion." TFEB both regulates autophagy and is a "key player in lipid metabolism," they added.

Funders included the American Heart Association, American Diabetes Association, and National Institutes of Health. The researchers reported no conflicts of interest.

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SOURCE: Qian Q et al. Cell Molec Gastroenterol Hepatol. doi: 10.1016/j.jcmgh.2019.03.005.

DR. DIWAN

Understanding the mechanisms for how obesity affects cellular pathways is critical for identifying therapeutic targets to prevent its adverse consequences. Qian et al., through a well-designed series of experiments conducted in a mouse model of diet-induced obesity, demonstrate localization of inducible nitric oxide synthase (iNOS) to lysosomes in the livers of obese animals. This triggers excess local NO generation, which leads to excessive nitrosylation of lysosomal proteins.

A direct consequence of the resultant lysosome dysfunction is impaired autophagy, which is a critical cellular pathway for clearing away damaged organelles and proteins and generating energy under nutrient stress. Their studies also implicate lysosomal NO generation in suppressing the activity of transcription factor EB, a master regulator of autophagy and lysosome biogenesis. Remarkably, genetic ablation of iNOS prevents the lysosome dysfunction and autophagy impairment, to attenuate obesity-induced insulin resistance. Future studies will be required to assess the mechanisms for iNOS localization to the lysosomes and its interplay with the mammalian target of rapamycin (mTOR) signaling pathway in the face of sustained nutrient excess.

Abhinav Diwan, MD, is an associate professor of medicine, cell biology, and physiology at Washington University and associate division chief of cardiology at the John Cochran VA Medical Center, both in St. Louis. He has no conflicts.

Not eating red, processed meat did not prevent CD flares

BY AMY KARON
MDedge News

For adults with Crohn's disease in remission at baseline, eating red and processed meat no more than once per month did not reduce risk of relapse in a randomized control trial.

After 49 weeks, there were no significant differences in time to relapse, time to moderate or severe relapse, or time to persistent relapse between the low- and high-meat groups, reported Lindsey G. Aldenberg, DO, of the Children's Hospital of Philadelphia and coinvestigators. The findings were published in Gastroenterology.

The randomized study included 213 adults with Crohn's disease whose short Crohn's Disease Activity Index (sCDAI) score was 150 or less at baseline and who consumed red meat at least once weekly. They were instructed to consume one serving (3 ounces) of red meat or any processed (smoked, salted, or otherwise preserved) meat at least twice weekly (high-meat group) or no more than once monthly (low-meat group). To create a placebo-like effect, all patients were told to drink at least 16 ounces of water daily. Each week, patients were emailed a web-based survey of disease status and dietary adherence. At baseline and during six other weeks, they also received a daily survey of disease activity and current medications. The primary outcome was symptomatic relapse, defined as at least a 70-point rise such that sCDAI score exceeded 150, surgery for Crohn's disease flare, or self-reported initiation or dose increase of mesalamine, thiopurine, methotrexate, corticosteroid, anti–tumor necrosis factor–alpha therapy, or natalizumab.

In all, 78% (166) of patients either completed the study or experienced an outcome. Symptomatic relapse occurred in 62% of these 166 patients, while 42% and 35% had moderate to severe relapses, respectively. "There were no significant differences in time to relapse for any of the outcomes," the researchers wrote. Results were similar when they assumed that patients who completed no surveys all relapsed at week 1.

Continued on following page

DR. QUIGLEY

For understandable reasons, many patients believe that their symptoms or gastrointestinal disorders emanate from some interaction with a component of their diet. Crohn's disease is no exception; various dietary factors have been incriminated in disease pathogenesis and the induction of relapse among those already affected. Furthermore, a number of dietary strategies or interventions have been recommended as therapeutic. For the induction of relapse, meat and related dietary components, such as fat, have been primary suspects.

This association was examined in this study by comparing the effects of low- or high-meat intakes (red meat and processed meat) over 49 weeks on clinical relapse rates in Crohn's patients in remission at baseline. Sixty-two percent relapsed, and 42% had a moderate to severe relapse. However, there was no difference in time to relapse or rates of moderate/severe relapse between the two dietary groups.

Dietary intervention studies are notoriously difficult to perform; what is remarkable was that the investigators were able to complete the study with high rates of compliance over almost a year! Whether dietary patterns earlier in life (when the microbiota is more susceptible) or over longer periods could affect the natural history of inflammatory bowel disease remains to be determined. For now, this study has shown us that high-quality dietary studies can be performed and that variations in meat intake, within the range of those likely to occur in real life, do not affect relapse rates in Crohn's disease.

Eamonn M. Quigley, MD, is the David M. Underwood Chair of Medicine in Digestive Disorders, Institute for Academic Medicine; director, Lynda K. and David M. Underwood Center for Digestive Disorders, Houston Methodist Hospital. He has no relevant conflicts of interest.

AGA honors annual award winners at DDW reception

The annual AGA Recognition Awards honor the achievements of innovators and leaders in gastroenterology. During a reception at Digestive Disease Week® (DDW), AGA celebrated members who contribute to the profession.

"AGA members honor their colleagues and peers for outstanding contributions to the field of gastroenterology by nominating them for the AGA Recognition Awards," said AGA Institute Past President David A. Lieberman, MD, AGAF.

Julius Friedenwald Medal

AGA awarded its highest honor to John I. Allen, MD, MBA, AGAF, for contributions to the field of gastroenterology and to AGA that span decades. The Julius Friedenwald Medal, presented annually since 1941, recognizes a physician for lifelong contributions to the field of gastroenterology.

Dr. Allen is internationally renowned for bringing unique and critical knowledge about health care delivery and health care economics to the field of gastroenterology, as well as for his decades of AGA leadership. His experience includes private practice, nonacademic health systems, and leadership within two academic medical centers.

As AGA Institute President, Dr. Allen led the development of AGA's 5-year strategic plan and made AGA a national player at the federal, state, and local levels in a time of massive health care delivery transformation. He is clinical professor of medicine in the division of gastroenterology and hepatology and chief clinical officer of the University of Michigan Medical Group at the University of Michigan School of Medicine, Ann Arbor.

Distinguished Achievement Award in Basic Science

AGA honored Harry B. Greenberg, MD, with the AGA Distinguished Achievement Award in Basic Science for work that has significantly advanced the science and practice of gastroenterology. Dr. Greenberg's contributions over several decades contributed to the development of rotavirus vaccines and an increased understanding of viral pathogenesis, particularly rotavirus, norovirus and hepatitis. Dr. Greenberg is an associate dean for research at the Stanford University School of Medicine, Palo Alto, Calif.

William Beaumont Prize in Gastroenterology

AGA awarded Timothy C. Wang, MD, AGAF, the William Beaumont Prize in Gastroenterology, which recognizes an individual who has made a unique, outstanding contribution of major importance to the field of gastroenterology. Dr. Wang's contributions to the understanding and practice of modern gastroenterology and digestive science are exemplified through his work, which includes defining the mechanisms and cellular origins of Barrett's esophagus and gastroesophageal cancer.

Dr. Wang has served AGA in numerous positions, including as president of the AGA Institute, is chief of the division of digestive and liver diseases at the Columbia University Medical Center and the Dorothy L. and Daniel H. Silberberg Professor of Medicine at the Columbia University Vagelos College of Physicians and Surgeons, New York.

Distinguished Educator Award

AGA recognized Deborah D. Proctor, MD, AGAF, with the Distinguished Educator Award, which honors an individual who has made outstanding contributions as an educator in gastroenterology on the local and national level. Dr. Proctor is a national expert in gastroenterology training and education who has taught and inspired generations of future gastroenterologists, nurses and physician assistants.

Dr. Proctor currently serves as the AGA Institute Education & Training Councillor. She is professor of medicine and the medical director of the inflammatory bowel disease program at the Yale School of Medicine, New Haven, Conn.

Distinguished Clinician Awards

The AGA Distinguished Clinician Awards honor members of the practicing community who, by example, combine the art of medicine with the skills demanded by the scientific body of knowledge in service to their patients.

AGA presented the **Distinguished Clinician Award, Private Practice**, to Naresh T. Gunaratnam, MD, AGAF. Dr. Gunaratnam has made a significant impact on patient care in his community and improved gastroenterology-oncology care by creating the Endoscopic Ultrasound & Interventional GI Program at St. Joseph Mercy Ann Arbor Hospital in Ypsilanti, Mich. Dr. Gunaratnam is director of research and obesity management at Huron Gastro, Ypsilanti.

AGA presented the **Distinguished Clinician Award, Clinical Academic Practice,** to Edward V. Loftus Jr., MD, AGAF. Dr. Loftus is recognized as a role model in practice and an effective researcher. He's known for his devotion to treating patients with ulcerative colitis and Crohn's disease with high-quality clinical care, including understanding the predictors of treatment response. Dr. Loftus is a practicing gastroenterologist and professor of medicine at the Mayo Clinic College of Medicine and Science, Rochester, Minn.

Distinguished Mentor Award

The Distinguished Mentor Award was presented to Fred S. Gorelick, MD. The award recognizes an individual who has made contributions to the mentoring of trainees in the field of gastroenterology and for achievements as an outstanding mentor throughout a career. Dr. Gorelick has been an inspiration to generations of trainees, many of whom have gone on to successful academic careers as faculty members, section chiefs, program directors, department chairs, and institute directors. Dr. Gorelick is professor of medicine and cell biology at Yale School of Medicine and deputy director of the Yale MD, PhD Program, New Haven, Conn.

Research Service Award

Ann G. Zauber, PhD, received the Research Service Award, which honors individuals whose work has significantly advanced gastroenterological science and research. Dr. Zauber's accomplishments have changed and advanced the practice of gastroenterology. Her research involving colorectal cancer screening and surveillance studies has had far-reaching effects on public policy. She is well known for her leadership role in the development of colorectal cancer screening guidelines, which have significantly reduced mortality and incidence rates. Dr. Zauber is attending biostatistician in the department of epidemiology and biostatistics at Memorial Sloan Kettering Cancer Center, New York.

Young Investigator Award

The AGA Young Investigator Award recognizes two young investigators, one in basic science and one in clinical science, for outstanding research achievements.

AGA honored Sonia S. Kupfer, MD, with the **Young Investigator Award in Clinical Science.** Dr. Kupfer is nationally and internationally recognized as an expert in colorectal cancer in high-risk populations, such as individuals with hereditary cancer syndromes and African Americans. During her clinical and translation-

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Continued from previous page

At week 20, median fecal calprotectin levels were higher in the high-meat arm (74.5 mcg/g) than in the low-meat arm (36.0 mcg/g), but the difference was not statistically significant. Proportions of patients with fecal calprotectin levels above 150 or 250 mcg/g also did not significantly differ between arms.

Adherence to the diets was reasonable: Patients in the high-meat group reported consuming at least two servings of red or processed meat during 98.5% of weeks, while patients in the low-meat arm completely abstained from red or processed meat during 57.3% of weeks. A logistic regression model showed that the high-meat group was much more likely to consume a least two servings of red or processed meat in the prior week than the low-meat group (*P* less than .0001). Approximately 90% of patients in both arms drank the recommended amount of water.

Study participants were part of IBD Partners, an Internet-based cohort of more than 15,000 patients with inflammatory bowel disease.

"Based on these results, there is insufficient evidence to recommend reduction of red and processed meat consumption solely for the purpose of improving Crohn's disease outcomes, although there may be some benefit for other health conditions," Dr. Aldenberg and associates concluded.

The Crohn's and Colitis Foundation and the National Institutes of Health supported the work. Dr. Aldenberg disclosed receiving research funding from Seres Therapeutics. Two of six coinvestigators disclosed ties to Nestle Health Science, AbbVie, Pfizer, Eli Lilly, and several other pharmaceutical companies.

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SOURCE: Aldenberg LG et al. Gastroenterology. 2019 Mar 11. doi: 10.1053/j.gastro.2019.03.015.

al research to better understand factors that increase the risk of colorectal cancer, Dr. Kupfer identified distinctions in the African American population compared with whites. Dr. Kupfer is director of the Gastrointestinal Cancer Risk and Prevention Clinic and associate professor of medicine at the University of Chicago.

AGA honored Costas A. Lyssiotis, PhD, with the **Young Investigator Award in Basic Science.** His research, work ethic, and innovative approaches have made him a distinguished leader in the study of pancreatic cancer. His work has broad implications for harnessing the power of the immune system to treat disease, and his laboratory is working to develop drug therapies that target a pancreatic cancer metabolism-specific enzyme. Dr. Lyssiotis is assistant professor in the department of molecular and integrative physiology in the division of gastroenterology at the University of Michigan Medical School, Ann Arbor.

2019 Research Mentor Award

The AGA Institute also presented Council Section Research Mentor Awards during section-sponsored sessions at DDW®. These awards recognize AGA members for their achievements as outstanding mentors in a specific area of research. Here are the 2019 Research Mentor Award recipients:

- **Basic & Clinical Intestinal Disorders**

Wayne I. Lencer, MD, AGAF
Harvard Medical School Pediatrics, Boston, Mass.

- **Cellular & Molecular Gastroenterology**

Mark Donowitz, MD, AGAF
Hopkins Center for Epithelial Disorders, Hopkins NIH Conte Digestive Diseases Basic & Translational Research Core Center, Johns Hopkins University School of Medicine, Baltimore, Md.

- **Clinical Practice**

Linda Rabeneck, MD, MPH
Cancer Care Ontario, University of Toronto

- **Esophageal, Gastric & Duodenal Disorders**

Stuart Jon Spechler, MD, AGAF
Baylor University Medical Center at Dallas; Center for Esophageal Research Baylor Scott & White Research Institute, Dallas, Tex.

- **Gastrointestinal Oncology**

Richard M. Peek Jr., MD, AGAF
Vanderbilt University School of Medicine, Nashville, Tenn.

- **Imaging, Endoscopy & Advanced Technology**

Irving Waxman, MD
University of Chicago, Ill.

- **Immunology, Microbiology & Inflammatory Bowel Diseases**

Edward V. Loftus Jr., MD, AGAF
Mayo Clinic, Rochester, Minn.

- **Liver & Biliary**

David A. Brenner, MD
University of California San Diego School of Medicine, Calif.

- **Microbiome & Microbial Therapy**

R. Balfour Sartor, MD
University of North Carolina School of Medicine, Chapel Hill

- **Neurogastroenterology & Motility**

Gianrico Farrugia, MD, AGAF
Mayo Clinic, Jacksonville, Fla.

- **Obesity, Metabolism & Nutrition**

Kelly A. Tappenden, PhD, RD
University of Illinois, Chicago

- **Pancreatic Disorders**

Fred S. Gorelick, MD
West Haven VA Medical Center, Conn.

- **Pediatric Gastroenterology & Developmental Biology**

Anne Marie Griffiths, MD
The Hospital for Sick Children, Toronto

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Washington makes low drug prices a priority

The House of Representatives passed two bills aimed at speeding up the development of generics and biosimilars while the Trump administration finalized a rule to require drug companies to list the price of their products in their television ads.

The House passed two bills to address drug pricing. The House passed H.R. 1503, the Orange Book Transparency Act of 2019, legislation that would make changes to the FDA's "orange" book to provide better information on brand drug and patent exclusivity. The orange book is used by doctors and pharmacists for information on generic drug approvals and availability. It is also used by generic drug manufacturers to make decisions on where to invest in research and development as it provides information on the exclusivity period for brand name drugs. Similarly, the House passed H.R. 1520, the Purple Book Continuity Act, legislation that would update FDA's "purple" book on patents and exclusivity for biologics. These are the first bills of the 116th Congress to pass that address the costs of drugs.

The Administration finalizes rule on drug costs in advertising. The Trump administration finalized a rule that would require drug manufacturers to disclose prices on their products in television advertisements. Manufacturers must list a product's monthly wholesale price or the cost of a typical treatment if it is greater than $35 for 30 days. The information must appear in text large enough for people to read it and should also include a statement that people with insurance may pay a different amount for the product. The rule takes effect in 60 days and the drug industry opposes the rule, which they say could sway patients away from certain medications and lead to more misinformation on the actual costs.

House Appropriations Committee approves $2 billion NIH increase. The House Appropriations Committee approved their fiscal year 2020 Labor, HHS, and Education Appropriations bill that includes a $2 billion increase in NIH funding. The Committee also includes critical report language on several GI research areas including inflammatory bowel disease, colorectal cancer screenings, early-onset colorectal cancer, and the role of food as medicine in treating diseases. The bill also includes important language directing CMS to require Medicare Advantage plans to exclude from prior authorization requirements those services that align with evidence-based guidelines and have a high prior authorization approval rate. The language also calls for more transparency for Medicare Advantage plans with prior authorization so physicians are aware of what services require it.

Medical Nutrition Equity Act introduced in House. Rep. Jim McGovern, D-Mass., introduced H.R. 2501, the Medical Nutrition Equity Act, legislation that would mandate coverage of medically necessary foods for individuals with digestive and inherited metabolic disorders. AGA is supportive of this legislation that is critical for patients with digestive diseases and ensures their access to these lifesaving products.

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Physician innovator working to bring new tech to patients, thanks to AGA funding

The AGA Research Foundation's career development awards are invaluable tools for early-career investigators to advance their careers in gastroenterology and hepatology research. When Ashish Nimgaonkar, MD, MTech, MS, received the AGA-Boston Scientific Career Development Technology and Innovation Award in 2014, he was able to step up his research and develop a new technological approach for managing patients with chronic liver disease–related complications.


DR. NIMGAONKAR

We are delighted to introduce you to the work of Dr. Nimgaonkar, medical director in the Johns Hopkins Center for Bioengineering Innovation and Design, department of biomedical engineering, and an assistant professor of medicine and business at Johns Hopkins University.

Dr. Nimgaonkar's contributions to the field of gastroenterology, and to advancing care for patients with chronic liver disease, began in his small lab at Johns Hopkins University, Baltimore.

When Dr. Nimgaonkar received his funding from the AGA Research Foundation in 2014, he was able to focus on developing a technology that would enable patients with refractory ascites to manage their condition at home. This is a condition in which a large volume of fluid accumulates in the abdomen, causes difficulty breathing, and affects patients' quality of life. Patients visit a hospital or clinic several times a month to drain the fluid, which could weigh as much as 10 pounds or more. Refractory ascites is stubbornly resistant to standard medical therapy. The only definitive treatment is liver transplantation.

Dr. Nimgaonkar was able to combine his dual training in gastroenterology and in medical technology innovation through the biodesign program at Stanford (Calif.) University, along with the breadth of engineering and research expertise at Johns Hopkins University, to develop a bio-powered shunt that moves a patient's fluid buildup out of the peritoneal cavity to the urinary bladder, where it can be eliminated naturally. His shunt has another major advantage for patients who are on liver transplant lists and are required to undergo MRI and other diagnostics: It contains no metal components.

Read more and get to know Dr. Nimgaonkar at https://www.gastro.org/news/physician-innovator-working-to-bring-new-tech-to-patients-thanks-to-aga-funding.

ginews@gastro.org

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. Donate 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. Crohn's disease, infliximab and liver abscess (http://ow.ly/mTod50uyXCQ)
A 22-year-old Crohn's patient presented to the hospital in septic shock with acute renal failure due to pyogenic liver abscess, which had ruptured into the peritoneal cavity. Member seeks consult from the AGA Community on treatment options given this serious infection.

2. EUS-guided cholecystoenterostomy with LAMS (http://ow.ly/IqLP50uyXLg)
A member poses the question: How long should the stent stay in?

3. Colorectal cancer surveillance in Crohn's colitis and small duct PSC (http://ow.ly/tbe650uyXQh)

aga community

A member asks if you would continue yearly CRC surveillance on a patient with Crohn's colitis with very limited colonic involvement in the ascending colon, who is currently in clinical remission. The patient also has small duct PSC with early cirrhosis.

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

Pathway guides clinicians and referrals

IBD *from page 1*

tive, and a patient advocacy representative.

The pathway identifies the top three areas where IBD patients usually present with symptoms: the emergency department, primary care office, and gastroenterology office.

The work group developed a list of key characteristics associated with increased morbidity, established IBD, or IBD-related complications that can be separated into high-risk, moderate-risk, and low-risk groups to help clinicians determine the timing of and need for referrals.

The pathway uses a sample patient presenting with GI symptoms such as bloody diarrhea; GI bleeding; anemia; fecal urgency; fever; abdominal pain; weight loss; and pain, swelling, or redness in the joints. Clinicians then apply the key characteristics to triage the patients into the risk groups.

High-risk characteristics include history of perianal or severe rectal disease, or deep ulcers in the GI mucosa; two or more emergency department visits for GI problems within the past 6 months, severe anemia, inadequate response to outpatient IBD therapy, history of IBD-related surgery, and malnourishment.

Moderate-risk characteristics include anemia without clinical symptoms, chronic corticosteroid use, and no emergency department or other GI medical visits within the past year.

Low-risk characteristics include chronic narcotic use, one or more comorbidities (such as heart failure, active hepatitis B, oncologic malignancy, lupus, GI infections, primary sclerosing cholangitis, viral hepatitis, and celiac disease), one or more relevant mental health conditions (such as depression, anxiety, or chronic pain), and nonadherence to IBD medical therapies.

"Referrals should be based on the highest level of risk present, in the event that a patient has characteristics that fall in more than one risk category," the work group wrote.

To further guide clinicians in referring patients with possible or diagnosed IBD to gastroenterology specialists and to mental health and nutrition specialists, the work group developed an IBD Characteristics Assessment Checklist and a Referral Feedback form to accompany the pathway.

The checklist is designed for use by any health care professional to help identify whether a patient needs to be referred based on the key characteristics; the feedback form gives gastroenterologists a template to communicate with referring physicians about comanagement strategies for the patient.

The pathway also includes more details on how clinicians can tackle barriers to mental health and nutrition care for IBD patients.

"Until further evaluations are conducted, the work group encourages the immediate use of the pathway to begin addressing the needed improvements for IBD care coordination and communication between the different IBD providers," the authors wrote.

Dr. Kinnucan disclosed serving as a consultant for AbbVie, Janssen, and Pfizer and serving on the Patient Education Committee of the Crohn's and Colitis Foundation.

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SOURCE: Kinnucan J et al. Gastroenterology. 2019. doi: 10.1053/j.gastro.2019.03.064.

New donor rules outlined

Microbiota *from page 1*

developed infections caused by extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli*. One of the patients died.

"This is certainly a theoretical risk that we've known about," Lea Ann Chen, MD, a gastroenterologist at New York University, said in an interview. "This announcement is important, because we probably don't counsel patients specifically about this risk. We say there is a risk for transmission of infectious agents in general, but I think that probably very few counsel patients about a risk for transmission of MDROs."

The donor stool and FMT used in the two patients were not tested for ESBL-producing gram-negative organisms prior to use.

As a result of these serious adverse reactions, the FDA has determined that certain donor screening and stool testing protections are needed for any investigational use of FMT. On June 18, the agency released an additional statement, which stipulated that all Investigational New Drug (IND) holders must implement the following new requirements no later than July 15, 2019:

1. Donor screening must include questions that specifically address risk factors for colonization with MDROs, and individuals at higher risk of colonization with MDROs must be excluded from donation. Examples of persons at higher risk for colonization with MDROs include:

   a. Health care workers

   b. Persons who have recently been hospitalized or discharged from long-term care facilities

   c. Persons who regularly attend outpatient medical or surgical clinics

   d. Persons who have recently engaged in medical tourism

2. FMT donor stool testing must include MDRO testing to exclude use of stool that tests positive for MDRO. The MDRO tests should at minimum include ESBL-producing *Enterobacteriaceae*, vancomycin-resistant enterococci (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), and methicillin-resistant *Staphylococcus aureus* (MRSA). Culture of nasal or perirectal swabs is an acceptable alternative to stool testing for MRSA only. Bookend testing (no more than 60 days apart) before and after multiple stool donations is acceptable if stool samples are quarantined until the postdonation MDRO tests are confirmed negative.

3. All FMT products currently in storage for which the donor has not undergone screening and stool testing for MDROs as described above must be placed in quarantine until such time as the donor is confirmed to be not at increased risk of MDRO carriage and the FMT products have been tested and found negative. In the case of FMT products manufactured using pooled donations from a single donor, stored samples of the individual donations prior to pooling must be tested before the FMT products can be administered to subjects.

Dr. Lea Ann Chen said it's not that FMT is 'bad'; we just have to be more diligent about optimizing the safety of the procedure.

4. The informed consent process for subjects being treated with FMT product under your IND going forward should describe the risks of MDRO transmission and invasive infection as well as the measures implemented for donor screening and stool testing.

On June 14, the American Gastroenterological Association sent a communication about the FDA alert to its members, which stated that the AGA "is committed to advancing applications of the gut microbiome. Our top priority is ensuring patient safety from microbiome-based therapeutics, such as FMT. Through the AGA FMT National Registry, AGA is working with physicians and patients to track FMT usage, patient outcomes and adverse events. Associated with the registry is a biorepository of donor and patient stool samples, which will allow further investigation of unexpected events such as those described in FDA's safety alert."

Dr. Chen, who received the AGA Research Foundation's 2016 Research Scholar Award for her work on the gut microbiome and inflammatory bowel disease, pointed out that FMT has also been studied as a way to prevent colonization and infection with certain drug-resistant organisms, such as VRE.

"Therefore, it's not that FMT is 'bad;' we just have to be more diligent about optimizing the safety of the procedure by screening for of multidrug-resistant organisms," she said. "We also need to study the use of FMT more, so that we can fully understand the risks associated with the procedure. It's an important and potentially lifesaving procedure for some, but it's important that everyone go into the procedure understanding fully what the risks and benefits are."

Suspected adverse events related to the administration of FMT products can be reported to the FDA at 1-800-332-1088 or via MedWatch.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

FDA approves IB-Stim device for abdominal pain in IBS

BY MARY JO M. DALES
MDedge News

The IB-Stim device has been approved to aid in the reduction of functional abdominal pain in patients 11-18 years of age with irritable bowel syndrome (IBS), according to the U.S. Food and Drug Administration.

"This device offers a safe option for treatment of adolescents experiencing pain from IBS through the use of mild nerve stimulation," Carlos Peña, PhD, director of the Office of Neurological and Physical Medicine Devices in the FDA's Center for Devices and Radiological Health, said in a press release.

The prescription-only device has a single-use electrical nerve stimulator that is placed behind the patient's ear. Stimulating nerve bundles in and around the ear is thought to provide pain relief. The battery-powered chip of the device emits low-frequency electrical pulses continuously for 5 days, at which time it is replaced. Patients can use the device for up to 3 consecutive weeks to reduce functional abdominal pain associated with IBS.

The FDA reviewed data from 50 patients, aged 11-18 years, with IBS; 27 patients were treated with the device and 23 patients received a placebo device. The study measured change from baseline to the end of the third week in worst abdominal pain, usual pain, and Pain Frequency Severity Duration (PFSD) scores. Patients were allowed to continue stable doses of medication to treat chronic abdominal pain.

IB-Stim treatment resulted in at least a 30% decrease in usual pain at the end of 3 weeks in 52% of treated patients, compared with 30% of patients who received the placebo, and at least a 30% decrease in worst pain in 59% of treated patients, compared with 26% of patients who received the placebo.

The treatment group also had greater changes in composite PFSD scores at the end of 3 weeks. During the study, six patients reported mild ear discomfort, and three patients reported adhesive allergy at the site of application, according to the press release.

The device is contraindicated for patients with hemophilia, patients with cardiac pacemakers, or those diagnosed with psoriasis vulgaris.

The FDA granted marketing authorization of the IB-Stim to Innovative Health Solutions.

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Persistent fatigue plagues many IBD patients

BY DOUG BRUNK
MDedge News

REPORTING FROM DDW 2019

SAN DIEGO – Nearly two-thirds of patients with inflammatory bowel disease who initiate biologic therapy continue to experience persistent fatigue up to 1 year later, results from a prospective cohort study presented at the annual Digestive Disease Week® showed.


DR. BORREN

In an effort to define the trajectory of fatigue in IBD patients initiating treatment with infliximab, adalimumab, vedolizumab, or ustekinumab, lead study author Nynke Z. Borren, MD, and colleagues prospectively enrolled 206 patients with Crohn's disease and 120 patients with ulcerative colitis. Dr. Borren is a research fellow at the Massachusetts General Hospital Crohn's and Colitis Center, Boston.

They used the seven-point fatigue question in the Short Inflammatory Bowel Disease Questionnaire to define fatigue; a score of four or less for this question equaled fatigue. Next, they used multivariable regression models to examine the independent association between attainment of clinical remission and the resolution of fatigue.

Of the 326 patients, 134 initiated biologic therapy with infliximab or adalimumab, 129 with vedolizumab, and 63 with ustekinumab. Nearly two-thirds of patients (198, or 61%) reported significant fatigue at baseline, which was associated with female sex, depressive symptoms, and disturbed sleep (*P* less than .001). Those reporting significant fatigue at baseline also had higher disease activity scores, compared with those without fatigue (*P* less than .001).

Of the 198 patients who reported fatigue at baseline, 70% remained fatigued at week 14, while 63% remained fatigued at week 30, and 61% remained fatigued at week 54. The researchers observed no significant differences between the therapies in the proportion of patients who remained fatigued. In addition to disease activity, disturbed sleep at baseline was associated with fatigue at week 14 (odds ratio, 9.7) and at week 30 (OR, 3.7).

The researchers had no conflicts.

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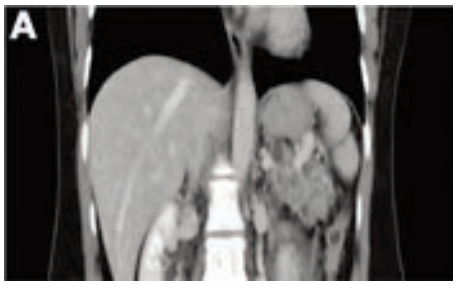
CLINICAL CHALLENGES AND IMAGES

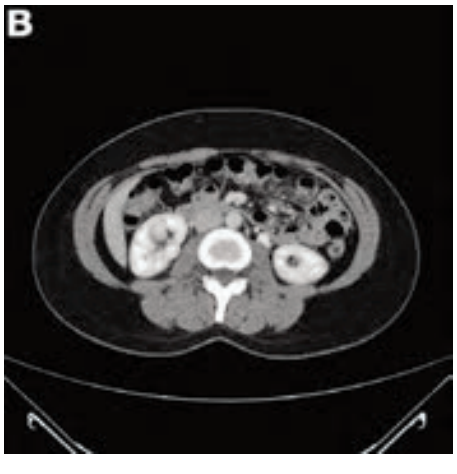
What's your diagnosis?

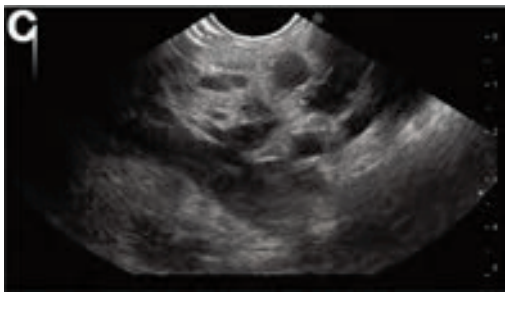
By Wai See Ma, MD, Hadi Moattar, MD, and Crispin Musumba, MBChB, PhD. Published previously in Gastroenterology (2018;154[4]:814-5).

A 32-year-old Filipino woman was referred for endoscopic ultrasound (EUS) imaging of the pancreas from another hospital where she had presented with a history of intermittent abdominal pain with radiation to the back precipitated by alcohol, and recurrent palpitations. During outpatient review before EUS, she gave a background history of previous laparoscopic ovarian cystectomy, as well as multiple previous admissions with supraventricular tachycardia requiring cardioversion on one occasion. One of her brothers had undergone brain surgery to remove a cyst, and another had died of an unspecified brain tumor at 25 years of age. Her mother had died of ovarian cancer.

Physical examination was unremarkable, with a normal pulse rate and blood pressure and no anemia, jaundice, or lymphadenopathy. Laboratory investigations including a full blood count, urea and electrolytes, liver function tests, thyroid function tests, and serum lipase were all normal. Abdominal computed tomography and ultrasound imaging revealed multiple cysts of varying sizes throughout the pancreas (Figure A), as well as multiple small benign-looking cysts in the liver. In addition, there was a 17-mm hyperdense solid lesion in the midpole of her right kidney visualized on computed tomography scan (Figure B). EUS revealed multiple thinly septated anechoic cysts throughout the pancreas, the largest measuring 36 mm located in the body, with no associated masses (Figure C).







AGA Institute

What is the likely diagnosis? What other investigations would you do for confirmation?

The diagnosis is on page 28.

Asymptomatic gallstones seldom require surgery

BY DOUG BRUNK
MDedge News

REPORTING FROM DDW 2019

SAN DIEGO – In patients with asymptomatic gallstones, the need for surgical intervention increases over time to 25%, according to results from a large, long-term analysis presented at the annual Digestive Disease Week®.

Lead study author Gareth Morris-Stiff, MD, PhD, of the department of general surgery at Cleveland Clinic, said that, while previous studies have evaluated the time to development of gallstone-related complications following identification of asymptomatic gallstones, factors associated with the need for surgical intervention in this population have not been documented. The current study aimed to perform a big data analysis to evaluate risk factors associated with intervention in asymptomatic gallstones and to develop a risk stratification tool to aid in predicting when individuals were likely to need future intervention for their gallstones.

DOUG BRUNK/MDEDGE NEWS

Dr. Gareth Morris-Stiff and coworkers developed a web-based risk score.

The researchers included Cleveland Clinic patients with CT/US reports containing "cholelithiasis" or "gallstones" between January 1996 and December 2016. Patients were excluded if they had a concurrent or prior event, had an event within 2 months, or lacked follow-up. Data collection included demographic characteristics, comorbid conditions or surgeries, imaging features, and medication use.

Dr. Morris-Stiff and his colleagues constructed Kaplan-Meier curves to analyze time to intervention and calculated cumulative incidence ratios. They used automated forward stepwise competing risk regression to create their model and receiver operating characteristics curves to analyze it.

Of the 49,414 patients identified with asymptomatic gallstones, 22,257 met criteria for analysis. About half (51%) were female, their mean age was 61 years, 80% were white, 16% were black, and the rest were from other racial/ethnic groups. The median follow-up was 4.5 years; for those undergoing intervention, 3.9 years. This translated to 112,111 total years of observation.

The researchers found that the cumulative incidence of intervention at 15 years was 25% and it increased linearly from the time of initial diagnosis of gallstones. A total of 1,762 patients (7.9%) underwent a surgical procedure, most often cholecystectomy (5.7%). Three factors were associated with reduced risk for surgical intervention: increasing age (hazard ratio, 0.94; *P* less than 0.001), male sex (HR, 0.78; *P* less than 0.001), and statin use (HR, 0.67; *P* less than 0.001).

Patient variables associated with increased need for surgical intervention included obesity (HR, 1.44; *P* less than 0.001) and having a hemolytic disorder (HR, 2.42; *P* less than 0.001). Gallstone-specific characteristics that increased the need for surgical intervention included a stone size greater than 9 mm (HR, 1.56; *P* less than 0.001), the presence of sludge (HR, 1.46; *P* less than 0.001), the presence of a polyp (HR, 1.68; *P* less than 0.001), and multiple stones (HR, 1.69; *P* less than 0.001).

Dr. Morris-Stiff and colleagues generated a web-based risk score to reliably identify these patients and provide prognostic information for counseling. A smartphone app based on the score is being developed. The researchers reported having no financial disclosures.

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Early cholecystectomy prevents recurrent biliary events

BY KARI OAKES
MDedge News

REPORTING FROM DDW 2019

SAN DIEGO – Waiting to perform cholecystectomy after mild biliary pancreatitis was associated with an increased risk of recurrent biliary events in a recent study. In a retrospective study of 234 patients admitted for gallstone pancreatitis, almost 90% of recurrent biliary events occurred in patients who did not receive a cholecystectomy within 60 days of hospital discharge. The overall rate of recurrence was 19%, and over half of patients (59%) did not receive a cholecystectomy during their index hospitalization.

Additionally, none of the recurrent biliary events occurred in those patients who did receive a cholecystectomy during the index hospitalization or within the first 30 days after discharge. "It really is the case that, 'if you snooze, you lose,' " said Vijay Dalapathi, MD, presenting the findings during an oral presentation at the annual Digestive Disease Week®.

Dr. Dalapathi and colleagues had observed that cholecystectomy during an index hospitalization for mild biliary pancreatitis was a far from universal practice. To delve further into practice patterns, Dr. Dalapathi, first author Mohammed Ullah, MD, and their coauthors at the University of Rochester (N.Y.) conducted a single-site retrospective study of patients who were admitted with gallstone pancreatitis over a 5-year period ending December 2017.

The study had twin primary outcome measures: cholecystectomy rates performed during an index hospitalization for gallstone pancreatitis and recurrent biliary events after hospitalization. Adult patients were included if they had a diagnosis of acute gallstone pancreatitis, with or without recurrent cholangitis, choledocholithiasis, or acute cholecystitis. Pediatric patients and those with prior cholecystectomy were excluded.

A total of 234 patients were included in the study. Their mean age was 58.3 years, and patients were mostly female (57.3%) and white (91.5%). Mean body mass index was 29.1 kg/m^2. A total of 175 patients (74.8%) had endoscopic retrograde cholangiopancreatography.

Of the entire cohort of patients, 138 (59%) did not have a cholecystectomy during the index hospitalization. Among the patients who did not receive a cholecystectomy, 33 (24%) were deemed unsuitable candidates for the procedure, either because they were critically ill or because they were poor candidates for surgery for other reasons. No reason was provided for the nonperformance of cholecystectomy for an additional 28 patients (20%).

The remaining 75 patients (54%) were deferred to outpatient management. Looking at this subgroup of patients, Dr. Dalapathi and his coinvestigators tracked the amount of time that passed before cholecystectomy.

The researchers found that 19 patients (25%) had not had a cholecystectomy within the study period. A total of 21 patients (28%) had the procedure more than 60 days from hospitalization, and another 23 (31%) had the procedure between 30 and 60 days after hospitalization. Just 12 patients (16%) of this subgroup had their cholecystectomy within 30 days of hospitalization.

Among patients who were discharged without a cholecystectomy, Dr. Dalapathi and his coauthors found 26 recurrent biliary events (19%): 15 were gallstone pancreatitis, and 10 were cholecystitis; 1 patient developed cholangitis.

The crux of the study's findings came when the investigators looked at the association between recurrent events and cholecystectomy timing. They found no recurrent biliary events among those who received cholecystectomy while hospitalized or within the first 30 days after discharge. Of the 26 events, 3 (12%) occurred in those whose cholecystectomies came 30-60 days after discharge. The remaining 23 events (88%) were seen in those receiving a cholecystectomy more than 60 days after discharge, or not at all.

Guidelines from the American Gastroenterological Association, the Society of American Gastrointestinal and Endoscopic Surgeons, and the American College of Gastroenterology recommend early cholecystectomy after mild acute gallstone pancreatitis, said Dr. Dalapathi.

"Cholecystectomy should be performed during index hospitalization or as soon as possible within 30 days of mild biliary pancreatitis to minimize risk of recurrent biliary events," said Dr. Dalapathi.

The authors reported no outside sources of funding and no conflicts of interest.

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SOURCE: Ullah M et al. DDW 2019, Abstract 24.

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AGA CLINICAL PRACTICE UPDATE

Management of coagulation in cirrhosis

BY AMY KARON
MDedge News

Cirrhosis can involve "precarious" changes in hemostatic pathways that tip the scales toward either bleeding or hypercoagulation, experts wrote in an American Gastroenterological Association Clinical Practice Update.

Based on current evidence, clinicians should not routinely correct thrombocytopenia and coagulopathy in patients with cirrhosis prior to low-risk procedures, such as therapeutic paracentesis, thoracentesis, and routine upper endoscopy for variceal ligation, Jacqueline G. O'Leary, MD, AGAF, of Dallas VA Medical Center and her three coreviewers wrote in Gastroenterology.

For optimal clot formation prior to high-risk procedures, and in patients with active bleeding, a platelet count above 50,000 per mcL is still recommended. However, it may be more meaningful to couple that platelet target with a fibrinogen level above 120 mg/dL rather than rely on the international normalized ratio (INR), the experts wrote. Not only does INR vary significantly depending on which thromboplastin is used in the test, but "correcting" INR with a fresh frozen plasma infusion does not affect thrombin production and worsens portal hypertension. Using cryoprecipitate to replenish fibrinogen has less impact on portal hypertension. "Global tests of clot formation, such as rotational thromboelastometry (ROTEM), thromboelastography (TEG), sonorheometry, and thrombin generation may eventually have a role in the evaluation of clotting in patients with cirrhosis but currently lack validated target levels," the experts wrote.

They advised clinicians to limit the use of blood products (such as fresh frozen plasma and pooled platelet transfusions) because of cost and the risk of exacerbated portal hypertension, infection, and immunologic complications. For severe anemia and uremia, red blood cell transfusion (250 mL) can be considered. Platelet-rich plasma from one donor is less immunologically risky than a pooled platelet transfusion. Thrombopoietin agonists are "a good alternative" to platelet transfusion but require about 10 days for response. Alternative prothrombotic therapies include oral thrombopoietin receptor agonists (avatrombopag and lusutrombopag) to boost platelet count before an invasive procedure, antifibrinolytic therapy (aminocaproic acid and tranexamic acid) for persistent bleeding from mucosal oozing or puncture wounds. Desmopressin should be considered only for patients with comorbid renal failure.

For anticoagulation, the practice update recommends considering systemic heparin infusion for cirrhotic patients with symptomatic deep venous thrombosis (DVT) or portal vein thrombosis (PVT). However, the anti–factor Xa assay will not reliably monitor response if patients have low liver-derived antithrombin III (heparin cofactor). "With newly diagnosed PVT, the decision to intervene with directed therapy rests on the extent of the thrombosis, presence or absence of attributable symptoms, and the risk of bleeding and falls," the experts stated.

Six-month follow-up imaging is recommended to assess anticoagulation efficacy. More frequent imaging can be considered for PVT patients considered at high risk for therapeutic anticoagulation. If clots do not fully resolve after 6 months of treatment, options including extending therapy with the same agent, switching to a different anticoagulant class, or receiving transjugular intrahepatic portosystemic shunt (TIPS). "The role for TIPS in PVT is evolving and may address complications like portal hypertensive bleeding, medically refractory clot, and the need for repeated banding after variceal bleeding," the experts noted.

Prophylaxis of DVT is recommended for all hospitalized patients with cirrhosis. Vitamin K antagonists and direct-acting oral anticoagulants (dabigatran, apixaban, rivaroxaban, and edoxaban) are alternatives to heparin for anticoagulation of cirrhotic patients with either PVT and DVT, the experts wrote. However, DOACs are not recommended for most Child-Pugh B patients or for any Child-Pugh C patients.

No funding sources or conflicts of interest were reported.

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SOURCE: O'Leary JG et al. Gastroenterology. 2019. doi: 10.1053/j.gastro.2019.03.070.

Early TIPS shows superiority to standard care for advanced cirrhosis with acute variceal bleeding

BY WILL PASS
MDedge News

For patients with advanced cirrhosis and acute variceal bleeding, early treatment with transjugular intrahepatic portosystemic shunt (TIPS) appears to improve transplantation-free survival, according to investigators.

Early TIPS "should therefore be preferred to the current standard of care," reported lead author Yong Lv, MD, of the Fourth Military Medical University in Xi'an, China, and colleagues, referring to standard pharmaceutical and endoscopic therapy.

"[The current standard] approach has improved patient outcomes," the investigators wrote in the Lancet Gastroenterology & Hepatology. "However, up to 10%-20% of patients still experience treatment failure, requiring further intensive management. In such patients, [TIPS] is successful in achieving hemostasis in 90%-100% of patients. However, 6-week mortality remains high [35%-55%]. This is probably because the severity of the underlying liver disease has worsened and additional organ dysfunction may have occurred after several failed endoscopic therapy attempts."

Previous studies have explored earlier intervention with TIPS; however, according to the investigators, these trials were inconclusive for various reasons. For example, uncovered stents and an out-of-date control therapy were employed in a trial by Monescillo et al., while a study by Garcia-Pagan et al. lacked a primary survival endpoint and has been criticized for selection bias. "Thus, whether early TIPS confers a survival benefit in a broader population remains to be assessed," the investigators wrote.

To this end, the investigators screened 373 patients with advanced cirrhosis (Child-Pugh class B or C) and acute variceal bleeding. Of these, 132 were eligible for inclusion based on age, disease severity, willingness to participate, comorbidities, and other factors. Patients were randomized 2:1 to receive either early TIPS or standard therapy.

Within 12 hours of hospital admission for the initial bleeding episode, all patients received vasoactive drugs or endoscopic band ligation and prophylactic antibiotics. Control patients continued vasoactive drugs for up to 5 days, followed by propranolol, which was titrated to reduce resting heart rate by 25% but not less than 55 beats per minute. Elective endoscopic band ligation was performed within 1-2 weeks of initial endoscopic treatment, then approximately every 2 weeks until variceal eradication, and additionally if varices reappeared. TIPS was allowed as rescue therapy. In contrast, patients in the TIPS group underwent the procedure with conscious sedation and local anesthesia within 72 hours of diagnostic endoscopy, followed by approximately 1 week of antibiotics and vasoactive drugs. TIPS revision with angioplasty or another stent placement was performed in the event of shunt dysfunction or reemergence of portal hypertensive complications. The final dataset contained 127 patients, as 3 were excluded after randomization because of exclusionary diagnoses, 1 withdrew consent, and 1 died before TIPS placement.

The primary endpoint was transplantation-free survival. The secondary endpoints were new or worsening ascites based on ultrasound score or sustained ascites

Continued on following page

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necessitating paracentesis, failure to control bleeding or rebleeding, overt hepatic encephalopathy, other complications of portal hypertension, and adverse events.

After a median follow-up of 24 months, data analysis showed a survival benefit associated with early TIPS based on multiple measures. Out of 84 patients in the TIPS group, 15 (18%) died during follow-up, compared with 15 (33%) in the control group. Actuarial transplantation-free survival was also better with TIPS instead of standard therapy at 6 weeks (99% vs. 84%), 1 year (86% vs. 73%), and 2 years (79% vs. 64%). The hazard ratio for transplantation-free survival was 0.50 in favor of TIPS (P = .04). These survival advantages were maintained regardless of hepatitis B virus status or Child-Pugh/Model for End-Stage Liver Disease score.

Similarly to transplantation-free survival, patients treated with TIPS were more likely to be free of uncontrolled bleeding or rebleeding at 1 year (89% vs. 66%) and 2 years (86% vs. 57%). The associated hazard ratio for this outcome favored early TIPS (HR, 0.26; P less than .0001), and univariate and multivariate analysis confirmed an independent protective role. In further support of superiority over standard therapy, patients treated with TIPS were more likely than those in the control group to be free of new or worsening ascites at 1 year (89% vs. 57%) and 2 years (81% vs. 54%).

No significant intergroup differences were found for rates of overt hepatic encephalopathy, hepatic hydrothorax, hepatorenal syndrome, spontaneous bacterial peritonitis, hepatocellular carcinoma, serious adverse events, or nonserious adverse events. At 1 and 3 months, patients in the TIPS group had a slight increase of median bilirubin concentrations and median international normalized ratio; however, these values normalized after 6 months. A similar temporal pattern was observed in early TIPS patients with regard to median Model for End-Stage Liver Disease score.

"[The transplantation-free survival benefit of early TIPS] was probably related to better control of factors contributing to death, such as failure to control bleeding or rebleeding or new or worsening ascites, without increasing the frequency and severity of overt hepatic encephalopathy and other adverse events," the investigators concluded. "This study provides direct evidence and greater confidence in the recommendations of current guidelines that early TIPS should be performed in high-risk patients without contraindications.

"Future studies addressing whether early TIPS can be equally recommended in Child-Pugh B and C patients are warranted," the investigators added.

The study was funded by the National Key Technology R&D Program, Boost Program of Xijing Hospital, Optimized Overall Project of Shaanxi Province, and National Natural Science Foundation of China. The investigators reported no conflicts of interest.

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SOURCE: Lv Y et al. Lancet Gastroenterol Hepatol. 2019 May 29. doi: 10.1016/S2468-1253(19)30090-1.

Meta-analysis finds no link between PPIs and dementia

BY DOUG BRUNK
MDedge News

REPORTING FROM DDW 2019

SAN DIEGO – There is no significant increased risk of dementia among patients who use proton pump inhibitors, compared with those who don't, results from a systematic meta-analysis suggest.

The finding runs counter to recent studies, including a large pharmacoepidemiological claims data analysis from Germany, that propose an association between proton pump inhibitor (PPI) use and the development of dementia (JAMA Neurol. 2016;73[4]:410-6). "The issue with these studies is that they're based on retrospective claims data and pharmacoepidemiological studies and insurance databases that don't really give you a good causality basis," lead study author Saad Alrajhi, MD, said in an interview at the annual Digestive Disease Week®.

In an effort to better characterize the association between PPI exposure and dementia, Dr. Alrajhi, a gastroenterology fellow at McGill University, Montreal, and colleagues conducted a meta-analysis of all fully published randomized clinical trials or observational studies comparing use of PPIs and occurrence of dementia. The researchers queried Embase, MEDLINE, and ISI Web of Knowledge for relevant studies that were published from 1995 through September 2018. Next, they assessed the quality of the studies by using the Cochrane risk assessment tool for RCTs or the Newcastle-Ottawa Scale for observational studies.

Key clinical point:
The incidence of dementia was not significantly increased among patients in the PPI-exposed group (OR, 1.08; 95% CI, 0.97-1.20; *P* = .18).

Doug Brunk/MDedge News

Dr. Saad Alrajhi said the databases on which the recent studies are based are not a good basis for causality.

As the primary outcome, the researchers compared dementia incidence after PPI exposure (experimental group) versus no PPI exposure (control group). Development of Alzheimer's dementia was a secondary outcome. Sensitivity analyses consisted of excluding one study at a time, and assessing results among studies of highest qualities. Subgroup analyses included stratifying patients by age. To report odds ratios, Dr. Alrajhi and colleagues used fixed or random effects models based on the absence or presence of heterogeneity.

Of 549 studies assessed, 5 met the criteria for inclusion in the final analysis: 3 case-control studies and 2 cohort studies, with a total of 472,933 patients. All of the studies scored 8 or 9 on the Newcastle-Ottawa scale, indicating high quality. Significant

Continued on following page

Coffee, tea, and soda all up GERD risk

BY KARI OAKES
MDedge News

REPORTING FROM DDW 2019

SAN DIEGO – Coffee, tea, and soda consumption are all associated with increased risk for gastroesophageal reflux disease (GERD), according to a new prospective cohort study presented at the annual Digestive Disease Week®.

In an interview, Raaj S. Mehta, MD, said that patients in his primary care panel at Massachusetts General Hospital, Boston, where he's a senior resident, frequently came to him with GERD. Patients frequently wanted to know which beverages might provoke or exacerbate their GERD.

In trying to help his patients, Dr. Mehta said he realized that there wasn't a prospective evidence base about beverages and GERD, so he and his colleagues used data from the Nurses' Health Study II (NHS II), a prospective cohort study, to look at the association between various beverages and the incidence of GERD.

"What's exciting is that we were able to find that coffee, tea, and soda – all three – increase your risk for [GERD]," Dr. Mehta said in a video interview. "At the highest quintile level, so looking at people who consume six or more cups per day, you're looking at maybe a 25%-35% increase in risk of reflux disease."

There was a dose-response relationship as well: "You do see a slight increase as you go from one cup, to two, to three, and so on, all the way up to six cups" of the offending beverages, said Dr. Mehta.

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Whether the beverages were caffeinated or not, said Dr. Raaj S. Mehta, made only a "minimal difference" in GERD risk.

Overall, the risk for GERD rose from 1.17 to 1.34 with coffee consumption as servings per day increased from less than one to six or more (*P* for trend less than .0001). Tea consumption was associated with increased GERD risk ranging from 1.08 to 1.26 as consumption rose (*P* for trend .001). For soda, the increased risk went from 1.12 at less than one serving daily, to 1.41 at four to five servings daily, and then fell to 1.29 at six or more daily servings (*P* for trend less than .0001).

Whether the beverages were caffeinated or not, said Dr. Mehta, made only a "minimal difference" in GERD risk. "In contrast, we didn't see an association for beverages like water, juice, and milk," he said – reassuring findings in light of fruit juice's anecdotal status as a GERD culprit.

The NHS II collected data every 2 years from 48,308 female nurses aged 42-62 years at the beginning of the study. Every 4 years dietary information was collected, and on the opposite 4-year cycle, participants answered questions about GERD. Medication use, including the incident use of proton pump inhibitors, was collected every 2 years. Patients with baseline GERD or use of PPIs or H_2 receptor antagonists were excluded from participation.

The quantity and type of beverages were assessed by food frequency questionnaires; other demographic, dietary, and medication variables were also gathered and used to adjust the statistical analysis.

A substitution analysis answered the question of the effect of substituting two glasses of plain water daily for either coffee, tea, or soda. Dr. Mehta and colleagues saw a modest reduction in risk for GERD with this strategy.

In addition to the prospective nature of the study (Abstract 514. doi: 10.1016/S0016-5085[19]37044-1), the large sample size, high follow-up rates, and well validated dietary data were all strengths, said Dr. Mehta. However, the study's population is relatively homogeneous, and residual confounding couldn't be excluded. Also, GERD was defined by self-report, though participants were asked to respond to clear, validated criteria.

Dr. Mehta reported no conflicts of interest.

Digestive Disease Week is jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy (ASGE), and the Society for Surgery of the Alimentary Tract (SSAT).

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AGA Resource
Encourage your patients to visit the AGA GI Patient Center for education by specialists for patients about GERD symptoms and treatments at https://www.gastro.org/practice-guidance/gi-patient-center/topic/gastro-esophageal-reflux-disease-gerd.

Continued from previous page

heterogeneity was noted for all analyses. The researchers found that the incidence of dementia was not significantly increased among patients in the PPI-exposed group (odd ratio, 1.08; 95% confidence interval, 0.97-1.20; *P* = .18). Sensitivity analyses confirmed the robustness of the results. Subgroup analysis showed no between-group differences among studies that included a minimum age above 65 years (three studies) or less than age 65 (two studies). PPI exposure was not associated with the development of Alzheimer's dementia (two studies) (OR, 1.32; 95% CI, 0.80-2.17; *P* = .27).

"In the absence of randomized trial evidence, a PPI prescribing approach based on appropriate utilization of guideline-based prescription should be done without the extra fear of the association of dementia," Dr. Alrajhi said.

The researchers reported having no financial disclosures.

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Artificial intelligence advances optical biopsy

BY KARI OAKES
MDedge News

REPORTING FROM DDW 2019

SAN DIEGO – Artificial intelligence is improving the accuracy of optical biopsies, a development that may ultimately void the need for tissue biopsies of many low-risk colonic polyps, Michael Byrne, MD, said at the annual Digestive Disease Week®.

Dr. Byrne, chief executive officer of Satisfai Health; Nicolas Guizard, a gastroenterologist at Vancouver General Hospital; and their colleagues have developed a "full clinical workflow" for detecting colonic polyps and performing optical biopsies of the polyps.

Using narrow band imaging (NBI) enhanced with artificial intelligence, the system was used to review 21,804 colonoscopy frames and it achieved a "near-perfect" diagnostic accuracy of 99.9%. In an assessment of colonoscopy videos that included 125 polyps, the system had 95.9% sensitivity, with a specificity of 91.6% and a negative predictive value of 93.6%, Dr. Byrne said.

The speed of the system's decision making is rapid, with a typical reaction time of 360 milliseconds. The system was able to make diagnostic inferences at a rate of 26 milliseconds per frame.

With exposure to more learning experiences, the artificial intelligence system improved and committed to a prediction for 97.6% of the polyps it visualized. Dr. Byrne said this result represented a 12.8% improvement from previously published data on the model's performance.

Dr. Byrne and his colleagues found the system had a tracking accuracy of 92.8%, meaning that this percentage of polyps was both correctly detected and assigned to a unique identifier for follow-up of the site of each excised polyp over time. The interface worked even when multiple polyps were seen on the same screen.

In a video interview, Dr. Byrne discussed the implications for

Continued on following page

DDSEP 9

Quick quiz answers

Q1. Correct answer: D

Rationale
Achalasia and pseudoachalasia are on the differential. Given the advanced age, progressive course, and significant weight loss, an endoscopy with careful attention to GEJ should be performed to rule out malignancy causing a pseudoachalasia presentation (answer D). Manometry should be done after the endoscopy to confirm and subtype the achalasia. If achalasia is confirmed and malignancy is ruled out, myotomy either with a modified Heller approach or peroral endoscopic myotomy would be appropriate in a surgically fit patient (answer A) and botulinum toxin may be considered in a poor surgical candidate. Medications such as calcium channel blockers and nitrates (answer C) are not definitive treatment options for achalasia and not warranted in malignancy. Additional information is needed on the diagnosis and prognosis prior to committing to a G tube (answer E).

Reference
Zaninotto G, Bennett C, Boeckxstaens G, et al. The 2018 ISDE achalasia guidelines. Dis Esophagus. 2018 Sep 1;31(9).

Q2. Correct answer: C

Rationale
Oral iron, and not infusions, are associated with peptic ulcer disease. Sumatriptan alone, or tamoxifen, are not known to cause ulcers.

Reference
Miyake K, Kusunoki M, Shinji Y, et al. Bisphosphonate increases risk of gastroduodenal ulcer in rheumatoid arthritis patients on long-term nonsteroidal anti-inflammatory drug therapy. J Gastroenterol. 2009;44(2):113.

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FDA clears modified endoscope connector

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has announced the clearance of a modified multi-patient-use endoscope connector, which was designed to reduce the risk of cross-contamination previously identified by the FDA.

In a letter published April 18, the FDA had written that the original version of the product, the Erbe USA ERBEFLO port connector, was the

The FDA approval of the modified ERBEFLO port connector is based on a review of the functional and simulated use testing of the modified device design.

only one of its type on the market that did not feature a method of backflow prevention, as recommended by new FDA guidelines. As such, the original ERBEFLO device did not adequately reduce the risk of cross-contamination; blood, stool, or other fluids from previous patients could travel through the endoscopy channels, contaminating the connector, tubing, and water bottle.

The FDA approval of the modified ERBEFLO port connector is based on a review of the functional and simulated use testing of the modified device design. The effectiveness of the device at reducing the risk of backflow and contamination is also supported by simulated testing.

Revised labeling included with the product identifies compatible endoscopes and accessories and provides warnings to ensure proper usage.

"The clearance of the modified ERBEFLO 24-hour use port connector provides another option for health care facilities whose staff understand and can fully implement the instructions for use to reduce the risk of cross-contamination and infection," the FDA said in the May 23 update letter.

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AGA Resource

The AGA Center for GI Innovation and Technology (https://www.gastro.org/aga-leadership/centers/aga-center-for-gi-innovation-and-technology) will continue to monitor this issue and encourages all GIs to follow the most up-to-date FDA guidance.

Continued from previous page

gastroenterology and plans for a clinical trial for rigorous testing of the model.

Satisfai Health is developing the AI colonoscopy technology. Dr. Byrne is a cofounder of ai4gi, which holds a technology codevelopment agreement with Olympus US.

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The problem's costs are real

Burnout *from page 1*

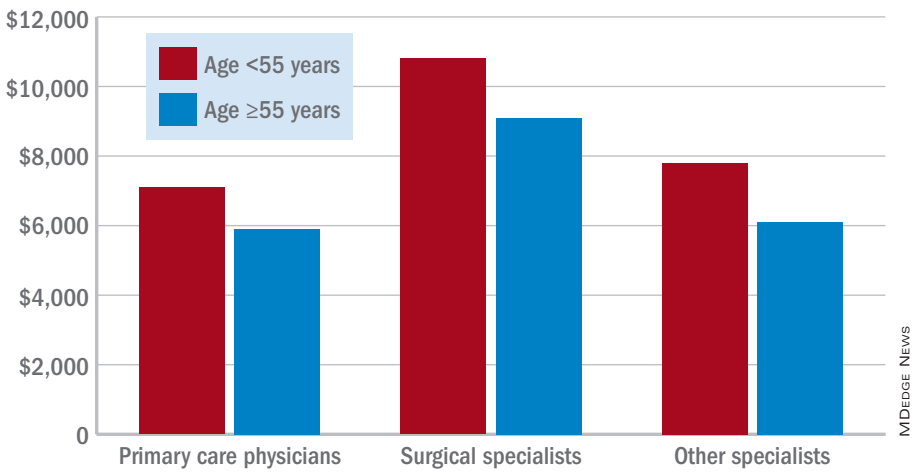
on two productivity metrics related to burnout – cost associated with physician replacement and lost income from unfilled physician positions. "Estimated turnover costs were generally higher than costs of reduced productivity across all" the various segments of age and specialty, Ms. Han and associates wrote.

"Burnout is a problem that extends beyond physicians to nurses and other health care staff. Future work holistically investigating the costs associated with burnout in health care organizations would be valuable. Studies focusing on differences in burnout-attributable costs across provider segments other than the ones investigated in this study, including academic versus private settings, or across a finer segmentation of physician specialties also might be fruitful," they wrote.

One investigator has received grants from the American Medical Association Accelerating Change in Medical Education Consortium, the Physicians Foundation, and the National Institutes of Health. Another received a startup grant from the National University of Singapore. Ms. Han said that she had no financial conflicts to disclose. All of the investigators' disclosures are available online.

AGA Resource
Learn practical tips to avoid physician burnout presented during an AGA symposium at DDW® at https://www.ddwnews.org/news/aga-symposium-provides-practical-tips-to-avoid-physician-burnout/.

Annual cost of burnout per employed physician, 2015



Note: The cost-consequence analysis used a mathematical model incorporating such inputs as burnout prevalence, turnover, replacement cost, and reduction in clinical hours.

Source: Ann Intern Med. 2019 May 28. doi: 10.7326/M18-1422

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SOURCE: Han S et al. Ann Intern Med. 2019 May 28. doi: 10.7326/M18-1422.

CMS seeks answers on prior authorization, other hassles to docs

BY GREGORY TWACHTMAN
MDedge News

Got an idea on how to reduce administrative burden to help reduce the cost of delivering health care? The Centers for Medicare & Medicaid Services wants to hear from you.

In a request for information published June 6, the agency seeks parties across the health care spectrum "to recommend further changes to rules, policies, and procedures that would shift more of clinicians' time and our health care system's resources from needless paperwork to high-quality care that improves patient health," CMS officials said in a statement.

The request for information, part of the agency's Patients Over Paperwork initiative, seeks suggestions on how to reduce hassles associated with reporting and documentation, coding, prior authorization, rural issues, dual eligible patients, enrollment/eligibility determination and the agency's own process for issuing regulations and policies.

CMS Administrator Seema Verma said in a statement. "Our goal is to ensure that doctors are spending more time with their patients and less time in administrative tasks."

The request for information was published in the Federal Register on June 11. Comments are due to the agency by Aug. 12. Comments can be made at www.regulations.gov and should refer to file code CMS-6082-NC.

AGA will submit comments to CMS on this issue given the huge burden that prior authorization plays in practices and the time that it takes away from providing care to patients. In the meantime, ask your legislator to support Improving Seniors Access to Timely Care Act of 2019, which was recently introduced in Congress to streamline the prior authorization process in the Medicare Advantage program to relieve the administrative burdens this poses for physicians and help patients receive quicker access to the medical care they need. Learn more at http://ow.ly/tJfX30oW5l7.

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SOURCE: Federal Register, CMS-6082-NC, https://federalregister.gov/d/2019-12215.

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 19: von Hippel-Lindau disease

The diagnosis is von Hippel-Lindau disease (VHL). Subsequent brain and renal magnetic resonance imaging showed features suggestive of a 5-mm right cerebellar hemangioblastoma and right renal cell carcinoma (RCC), respectively. Fundoscopy showed bilateral small retinal angiomas. Plasma and 24-hour urinary metenephrine levels were normal. Genetic testing confirmed a germline VHL mutation.

VHL is a rare autosomal-dominant hereditary multicancer condition characterized by germline mutations of the VHL tumor suppressor gene, with an incidence of 1 in 36,000 live births. The commonest associated tumors are retinal and central nervous system hemangioblastomas, RCC, pheochromocytoma, pancreatic islet cell tumors, and endolymphatic sac tumors.[1] Cystic lesions may also be seen in other viscera such as the liver and ovaries. Clinical diagnostic criteria require the presence of any of these tumors in a patient with a positive family history, or alternatively, at least two retinal or cerebellar hemangioblastomas, or one hemangioblastoma plus one visceral tumor.[2]

Pancreatic involvement occurs in 65%-77% of patients with VHL, and may be the sole manifestation in 7.6%. Findings include multiple true cysts (91%), microcystic serous cystadenomas (12%), solid pancreatic neuroendocrine tumors (5%-10%), or a combination (11.5%). Most lesions are asymptomatic, but may present with vague symptoms of epigastric pain, diarrhea, dyspepsia, obstructive jaundice, or endocrine and/or exocrine pancreatic insufficiency. Surgery is required for symptomatic cysts or large pancreatic neuroendocrine tumors. The main causes of death are RCC and central nervous system hemangioblastomas.[3] Our patient underwent laser therapy for her retinal angiomas, and is currently undergoing close regular surveillance. Clinicians should have a high index of suspicion for diagnosing VHL in patients with multiple pancreatic cysts. Because EUS is now widely used for the evaluation of pancreatic cysts, gastroenterologists may be first in making the diagnosis, as in this patient.

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PRACTICE MANAGEMENT TOOLBOX:

Prior authorization – a call to action

BY PATRICIA GARCIA, MD, AND SIMON C. MATHEWS, MD

Have you noticed that you and your staff are spending more time on prior authorization than in the past? Insurance companies are increasing the number of Current Procedural Terminology (CPT®) codes for services and procedures included in their prior authorization programs. More importantly, they are doing so without providing evidence that this approach improves patient safety or decreases unindicated medical procedures. There is also no transparency about how these prior authorization processes are developed, evaluated, or adjusted over time. Physicians and their staff are pushing back on social media, calling prior authorization programs a hassle and citing lengthy waits to speak to a physician reviewer who is often not even in their specialty.

Historically, insurers have used prior authorization to control costs, particularly those related to procedures and tests that may be inappropriately overutilized or no longer the standard of care; however, current activity suggests a much broader, indiscriminate approach. For example, insurers are requiring prior authorization for whole families of services and procedures. Anthem, the second largest insurance company in the United States, recently added the entire family of esophagogastroduodenoscopy (EGD) codes to its list of procedures requiring prior authorization in 10 states including Calif., Conn., Ind., Ohio, Ky., Mo., Nev., N.H., Va., and Wisc. A conversation earlier this year with the Anthem national prior authorization team revealed that they intend to keep adding codes for all specialties to their prior authorization program, portraying the process conducted by AIM Specialty Health® (a wholly owned subsidiary of Anthem), as fast, simple, and easy. However, many physicians and their office staff find the prior authorization process complex, time consuming, and frustrating.

Social media are rife with accounts from physicians who were forced to cancel planned procedures because the prior authorization process took weeks instead of days, received denials, and later found out that procedures were actually approved, or found themselves in peer-to-peer review with nonphysicians. Gastroenterologists have also reported cases of patients having flares of inflammatory bowel disease because of medication delays related to a cumbersome preauthorization process.

Because prior authorization impacts gastroenterologists' ability to provide timely care to patients, AGA and the entire physician community have been calling for regulatory change related to prior authorization in Medicare Advantage (MA) plans to reduce physician burden and enhance patient safety and care.

Last year, AGA worked with our congressional champions Reps. Phil Roe, MD (R-Tenn.), and Ami Bera, MD (D-Calif.), to secure 150 signatures on a letter to the CMS Administrator requesting the agency provide guidance to MA plans to ensure that prior authorization requirements do not create barriers to care.

One in every three people with Medicare is enrolled in a Medicare Advantage plan. Under current law, MA plans may not create inappropriate barriers to care that do not already exist within the original Medicare program. A recent survey by the American Medical Association found that over 90% of physician respondents felt that the prior authorization process led to delays in care for patients that could negatively impact clinical outcomes. AGA and other physician organizations are advocating for regulatory changes related to how MA plans use prior authorization.

In addition to our regulatory efforts, the AGA is working with members of Congress on legislative solutions to require the MA plans to increase transparency, streamline the prior authorization process, and minimize the impact on Medicare beneficiaries. With Dr. Bera, Reps. Susan DelBene, D-Wash., Mike Kelly, R-Penna., and Roger Marshall, R-Kans., introduced the Improving Seniors Timely Access to Care Act of 2019, legislation that would streamline the prior authorization process in the Medicare Advantage program to relieve the administrative burdens this poses for physicians and help patients receive quicker access to the medical care they need. Although this legislation addresses only MA plans, we are hopeful that this will be the first step in requiring health plans to streamline this process and ease administrative burden. Please help us increase support for this bill by contacting your legislators and asking that they cosponsor. It will take less than 5 minutes of your time and will have a significant effect, given the opposition we face from insurers: https://app.govpredict.com/portal/grassroots/campaigns/io77ozaa/take_action.

AGA and other physician organizations are advocating for regulatory changes related to how Medicare Advantage plans use prior authorization.

The AGA is working on your behalf to address prior authorization hassles with private payors, but to be effective we need to hear your experiences. We know private payors continue to develop more and more restrictive prior authorization policies covering an increasing number of services and procedures without evidence that these actions provide benefit to patients. Frequently, these policies are put into action without advance warning and your reports are the first signs we have that a change has been made. Reach out to the AGA via the AGA Community or Twitter to let us know what's happening. We will take your stories directly to the insurance companies and demand that they work with us to reduce physician burden and improve transparency.

You may also consider filing a complaint with the State Insurance Commissioner. State Insurance Commissioners are responsible for regulating the insurance industry in their state and can investigate to make sure the laws in their state are being followed and providers and patients are being treated fairly. While insurance law and regulation are established at the state

level, the insurance commissioners are members of the National Association of Insurance Commissioners (NAIC), which allows them to coordinate insurance regulation among the states and territories.

If you decide to file a complaint with your State Insurance Commissioner, first familiarize yourself with your state's complaint process. Many state insurance commissioners have a standard complaint form you can download or fill out online. Be sure to keep records of all conversations and interactions with the insurance company to document the steps you've taken to attempt to resolve the issue. Consider creating a log of the dates, times, and nature of your contact with the insurance company.

Once you have filed a complaint, the commissioner may send a copy to the insurance company and give them a date by which they must respond. If the commissioner believes the response is sufficient, she or he will send a copy of the insurance company's response to you. If the commissioner feels the insurance company's response is inadequate, staff from the commissioner's office will work with you and the insurer to resolve the issue.

While a report of one negative experience with an insurer may not be enough to illicit action, a pattern of delays and difficulties with an insurer's prior authorization process noted by many physicians is likely to catch an Insurance Commissioner's attention. The NAIC cannot tell a problem is widespread if providers and patients don't report it to the State Insurance Commissioners.

Please reach out to AGA with your stories about prior authorization problems, consider reporting insurance companies that employ systems that cause undue burden and delay to your State Insurance Commissioner and help us increase support for the Improving Seniors Timely Access to Care Act of 2019 by contacting your legislators and asking that they cosponsor using this link https://app.govpredict.com/portal/grassroots/campaigns/io77ozaa/take_action. Together, we can pressure insurers, Congress, and Medicare to relieve physician burden and help our patients receive the timely care they need.

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