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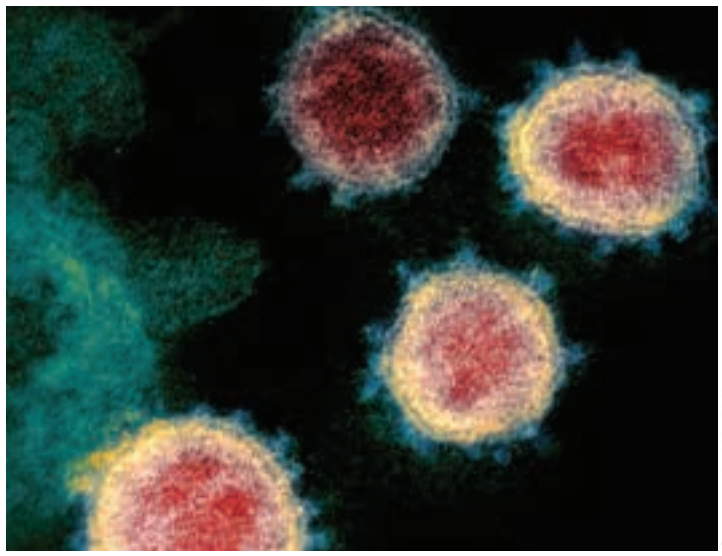

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Transmission electron microscope image shows SARS-CoV-2 – also known as 2019-nCoV, the virus that causes COVID-19.

AGA and sister societies issue insights for COVID-19

BY MARK S. LESNEY

MDedge News

Amid the growing SARS-CoV-2 pandemic, currently in its expansive growth phase in the United States, the American Gastroenterological Association (AGA), the American Association for the Study of Liver Diseases (AASLD), the American College of Gastroenterology (ACG), and the American Society for Gastrointestinal Endoscopy (ASGE) have jointly released "COVID-19 Clinical Insights for Our Community of Gastroenterologists and Gastroenterology Care Providers," which can be found on the websites of the various societies.

"The purpose of this communication is to jointly provide you with up to date COVID-19 information in order to maintain the highest level of health and safety for our patients, staff, community, and ourselves," according to the

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AGA guideline favors biologics for moderate/severe UC

Any biologic is superior to no treatment

BY RICHARD MARK KIRKNER

MDedge News

For moderate to severe ulcerative colitis, treatment with any one of the leading biologic agents is superior to no treatment at all. To maintain long-term remission, the Janus kinase (JAK) inhibitor tofacitinib 5 mg twice daily is preferred for most patients. And in treatment-naive patients, infliximab or vedolizumab should be used rather than adalimumab for inducing remission. These are key recommendations from the American Gastroenterological Association guideline for patients with moderate to severe ulcerative colitis (UC), published in Gastroenterology (doi: 10.1053/j.gastro.2020.01.006).

In all, the guideline comprises 11 recommendations for using immunomodulators, biologics, and small-molecule agents to induce and maintain remission in outpatients with moderate to severe UC and to decrease the need for colectomy in hospitalized patients with acute severe UC. The latest guideline follows a guideline for mild to moderate UC published last year (Gastroenterology.

See **Biologics** · *page 6*

Potential GI manifestation, transmission of novel coronavirus

BY JIM KLING

MDedge News

The novel coronavirus (2019-nCoV) shows evidence of causing gastrointestinal symptoms and has the potential to be transmitted by the fecal-oral route, according to a new report from physicians at Shanghai Jiao Tong University, published online (Gastroenterology. 2020 Mar 3. doi: 10.1053/j.gastro.2020.02.054).

The virus's respiratory symptoms are well documented and suggest primary transmission by droplet or contact, while other symptoms such as diarrhea, nausea, vomiting, and ab-

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LETTER FROM THE EDITOR:

Failure is not an option

Gene Kranz was the NASA Flight Director during the Gemini and Apollo space flights. He has written: "When bad things happened, we just calmly laid out all the options and failure was not one of them. We never panicked and we never gave up on finding a solution."


Dr. Allen

2019-nCoV will define this generation of health care providers. First identified in Wuhan, China, in December 2019 and first appearing in the United States on Jan. 19, 2020 (NEJM 2020;382:929). The U.S. Surgeon General and multiple endoscopy societies have recommended (strongly) that elective surgical and endoscopy procedures be deferred. Availability of testing has been slow, but many centers now have developed testing capabilities with 6-hour result turnaround. We do not know the full pathophysiology, R_0, ease of community transmission, risk to providers, definition of people at high risk, and much key information on which to base recommendations.

Health system and practice leaders do not yet have enough information to know which patients to defer, which patients should be seen, visitor policies, how to segregate waiting rooms, or how to protect providers. Despite a lack of definitive knowledge, we must make critical decisions and know that recommendations can change hourly. As the Chief Clinical Officer at Michigan Medicine, I am spending 16 hours a day immersed in these decisions and find that one of my critical jobs is to keep people from panicking.

Schools, bars, restaurants, churches, and other gathering places are closing. Three countries (to date) have instituted complete quarantine. Digestive Disease Week® has been canceled.

COVID-19 will define this generation. The public will also understand the real need for science, policies based on real facts, robust public health systems, and leaders who inspire confidence based on expert guidance. And, I believe we will see gastroenterologists, health systems, hospitals, and practices all showing us what our "finest hours" look like.

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

Tofacitinib recommended

Biologics *from page 1*

2019;156[3]:748-64). A technical review accompanied the most recent publication (Gastroenterology. 2020. doi: 10.1053/j.gastro.2020.01.007).

An updated guideline was long overdue, lead author Joseph D. Feuerstein, MD, of Beth Israel Deaconess Medical Center, Boston, said in an interview. "The care of patients with inflammatory bowel disease – both ulcerative colitis and Crohn's – has become increasingly complicated with many newer drugs becoming available," he said. "The paradigm of how we are treating the disease is evolving, but we haven't had updated, evidence-based guidelines." Dr. Feuerstein is the lead author of this guideline.

The guideline can also aid in influencing payers' policies that now require step-up therapy – that is, failing with the least costly drug before moving onto newer and more effective but costlier agents – Dr. Feuerstein said. "These guidelines show now that we should be treating people based on the evidence and not based on just an insurance company's preferred policy," he said.

The strongest recommendation is to use the tumor necrosis factor–alpha (TNF-alpha) antagonists infliximab, adalimumab, and golimumab; the anti-integrin agent vedolizumab; or the anti-interleukin 12/23 agent ustekinumab – all biologics – or the synthetic JAK inhibitor tofacitinib rather than not treating the UC.

'These guidelines show now that we should be treating people based on the evidence and not based on just an insurance company's preferred policy.'

This is the only recommendation labeled as "strong," based on "moderate quality evidence." The relative risk profiles the committee analyzed all favored the biologics over the JAK inhibitor.

Also based on moderate evidence is the recommendation to use infliximab or vedolizumab rather than adalimumab to induce remission in patients who had taken biologic agents before. The other recommendations are based on evidence listed at "low" or "very low" quality, or citing a "knowledge gap."

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"The quality of the evidence available is variable, and we can only make our recommendations based on the quality of the evidence there, but it doesn't negate the effects of the guideline itself," Dr. Feuerstein said. The strong recommendation is based on randomized clinical trials that led to the Food and Drug Administration approvals, said Aline Charabaty-Pishvaian, MD, AGAF, associate professor at Johns Hopkins University, Baltimore, and director of the Inflammatory Bowel Disease Center at Sibley Memorial Hospital, Washington. "For everything else, we do not have randomized controlled trials to help make a decision, and the recommendations are made based on the interpretation of different RCTs [randomized controlled trials], knowing that these trials have different designs, patient populations, and endpoints, as well as on experts' opinions," she said in an interview.

The only other recommendation based on moderate-quality evidence is to use infliximab or vedolizumab rather than adalimumab to induce remission in patients who haven't previously used biologic agents. The guideline also recommends using tofacitinib in these patients in the confines of a clinical trial; and using ustekinumab or tofacitinib rather than vedolizumab or adalimumab in patients who've already been on infliximab, particularly if they haven't responded to treatment.

The guideline also recommends against thiopurine monotherapy to induce remission, but, for maintenance of remission, recommends such treatment vs. none. However, the guideline suggests against methotrexate monotherapy to induce or maintain remission. And biologic monotherapy is preferred to thiopurine to induce remission, but the guideline makes no recommendation for biologic vs. thiopurine monotherapy to maintain remission. Likewise, combining vedolizumab or ustekinumab with thiopurines or methotrexate is preferred to monotherapy with either a biologic or thiopurine.

The guideline also addresses step-up therapy. It suggests biologics as a first treatment, either as monotherapy or in combination with an immunomodulator, rather than a step-up after failure with 5-aminosalicylates. Also, it recommends against continuing 5-aminosalicylates to induce or maintain remission after a patient has achieved remission with biologics as monotherapy or in combination with immunomodulators or tofacitinib.

The guideline also offers four recommendations for hospitalized patients with acute severe ulcerative colitis: use of intravenous 40-60 mg/d methylprednisolone rather than higher-dose IV corticosteroids, no adjunctive antibiotics in the absence of infection, use of infliximab or cyclosporine when IV corticosteroids fail, and no recommendation on the use of intensive vs. standard infliximab dosing when IV corticosteroids fail and the patient is already on infliximab.

The guideline also addresses step-up therapy. It suggests biologics as a first treatment, either as monotherapy or in combination with an immunomodulator, rather than a step-up after failure with 5-aminosalicylates.

The guideline will be meaningful in closing the evidence gap going forward because it can help direct the design of clinical trials, Dr. Charabaty-Pishvaian said. "The guideline highlights areas of need in terms of randomized clinical trials," she said. "We need these trials to answer the questions we ask ourselves in our daily practice when managing patients with UC: Which drug to choose as the first-line agent? Which drug is the second-line therapy when the disease doesn't respond or loses response to the first-line agent? Do we need to use combination therapy with all biologics, or only with anti-TNF-alpha agents? For how long? Can we use vedolizumab or ustekinumab as monotherapy when used as a first-line agent? And is there any advantage in adding an immunomodulator when these agents are used as third- or fourth-line therapy?"

Dr. Feuerstein has no relevant financial relationships to disclose. Guideline author Kim Isaacs, MD, disclosed relationships with AbbVie, Takeda, UCB, Janssen, and Hoffmann-Laroche. All other committee members have no relevant disclosures.

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SOURCE: Feuerstein JD et al. on behalf of the AGA Institute Clinical Guidelines Committee. Gastroenterology. 2020. doi: 10.1053/j.gastro.2020.01.006.

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Study: Gastric cancer predictors in Lynch syndrome

BY AMY KARON
MDedge News

Individuals with Lynch syndrome were significantly more likely to have a personal history of gastric cancer if they were older, were male, had an affected first-degree relative, or had pathogenic variants in the MLH1 or MSH2 mismatch repair genes, researchers reported.

"These findings suggest that personalized, risk-stratified approaches to gastric cancer surveillance may be appropriate for individuals with Lynch syndrome–associated mutations," wrote Jaihwan Kim of Seoul National University Bundang Hospital, Seongnam, South Korea, and associates. Their report is in Clinical Gastroenterology and Hepatology.

Lynch syndrome, which involves autosomal-dominant germline mutations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2) and EPCAM, significantly increases the risk for several types of cancer. Although Lynch syndrome increases gastric cancer risk almost 10-fold, more than 90% of individuals with Lynch syndrome do not develop it, the researchers noted. Given the lethality of this cancer, they sought to better characterize risk factors.

To do so, they studied cancer histories and clinical and demographic data from 51,086 individuals who were tested for gene variants associated with Lynch syndrome at a commercial laboratory between 2006 and 2013. More than 3,800 individuals had pathogenic variants, including more than 1,300 with mutations of MLH1, more than 1,600 with mutations of MSH2, 670 with mutations of MSH6, 145 with mutations in PMS2, and 28 with mutations in EPCAM. In all, 41 (1%) individuals with pathogenic mutations had a personal history of gastric cancer, while 350 (9%) had an affected first- or second-degree relative.

After the researchers controlled for potential confounders, males with Lynch syndrome–associated mutations had nearly triple the odds of a personal history of gastric cancer compared with females (odds ratio, 2.82; 95% CI, 1.48 - 5.38). The odds of gastric cancer also rose approximately 2-fold with each 10-year increase in age – and by 2.5-fold when individuals had an affected first-degree relative. Having a second-degree relative with gastric cancer was not an independent correlate. Compared with mutations in MSH6, PMS2, and EPCAM, gastric cancer was significantly more likely among individuals with mutations of MLH1 (OR, 6.53; 95% CI, 1.5 - 28.42) or MSH2 (OR, 5.23; 95% CI, 1.21 - 22.71).

Clinicians might use these factors to risk-stratify patients with Lynch syndrome to identify those who might benefit from enhanced surveillance with more frequent esophagogastroduodenoscopy, the researchers wrote. They noted that male sex, age, and first-degree family history increase the risk for sporadic gastric cancer unassociated with Lynch syndrome–associated mutations. Thus, these "traditional risk factors" might compound the inherited risk for gastric cancer observed in Lynch syndrome carriers.

The National Institutes of Health and the Pussycat Foundation Helen Gurley Brown Presidential Initiative provided funding. One coinvestigator disclosed a consulting relationship with Myriad Genetic Laboratories and having rights to an inventor portion of licensing revenues from PREMM5, a prediction model for Lynch syndrome mutations. The other researchers reported having no conflicts of interest.

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SOURCE: Kim J et al. Clin Gastroenterol Hepatol. 2019 Jul 15. doi: 1016/j.cgh.2019.07.012.

Pancreatic enzyme replacement flunked randomized trial

BY AMY KARON
MDedge News

Pancreatic enzyme replacement therapy (PERT) did not significantly alter body weight after pancreatoduodenectomy in the intention-to-treat analysis of a randomized, placebo-controlled trial.

After 3 months of treatment, the PERT group lost an average of 0.68 kg, and the placebo group lost an average of 1.19 kg ($P = .302$).

Although guidelines recommend PERT, doses and indications are not standardized because of insufficient data.

Low adherence might explain this missed primary endpoint – the 31% of patients who did not adhere to PERT were about four times more likely to lose weight, compared with patients who adhered to PERT (hazard ratio, 4.1, 95% confidence interval, 2.1-7.6), even after possible confounders were controlled for.

In the per-protocol analysis, PERT was associated with an average gain of 1.09 kg in body weight, whereas placebo was associated with an average loss of 2.28 kg ($P < .001$ for difference between groups). Therefore, clinicians should consider "active education and monitoring" to increase adherence to PERT among patients with pancreatic enzyme insufficiency after pancreatoduodenectomy, wrote Hongbeom Kim of Seoul (South Korea) National University College of Medicine. The findings were published in Clinical Gastroenterology and Hepatology.

Nutritional deficiencies, steatorrhea, bowel issues, and flatulence undermine health and quality of life among these patients, the researchers noted. Although guidelines recommend PERT, doses and indications are not standardized because of insufficient data. To date, most studies have focused on PERT for patients with pancreatic enzyme insufficiency attributable to chronic pancreatitis, not surgery.

This double-blind trial enrolled 304 patients who underwent pancreatoduodenectomy for benign or malignant indications at seven tertiary referral hospitals in South Korea. All patients had a preoperative or postoperative fecal elastase level of 200 mg/g or less.

Continued on following page

Dr. Ketwaroo

Pancreatic exocrine insufficiency after pancreatic surgery is a concern, and may be more severe in those undergoing pancreatoduodenectomy or with underlying chronic pancreatitis. Pancreatic enzyme replacement therapy is commonly used to treat PEI in chronic pancreatitis, but its role in postsurgical patients has not been fully defined.

In their study, Kim et al. enrolled patients with PEI after surgery, as defined by very low fecal elastase. Patients were then randomized to receive PERT vs. placebo for 3 months. In the intention-to-treat protocol, there was no difference between groups, which appears largely secondary to poor compliance with PERT. When PERT was used as prescribed, there was a statistically significant difference in weight change between groups but there was no impact on quality of life. This suggests that routine use of PERT in such patients is of questionable benefit – it is difficult to take (completed in less than half), and the weight loss it prevents may not have as much clinical effect as hoped.

However, there was an effect on nutritional levels (prealbumin), and patients were followed for only 3 months post surgery, whereas quality of life metrics or impact of better nutrition might be more apparent long term. Confounders that may have also limited the results include variable sensitivity of fecal elastase in detecting PEI, and a lower dose of PERT than is often used in clinical practice. Practically, it appears reasonable to discuss with patients the possibility of PEI after pancreatoduodenectomy and highlight that PERT can alter nutritional and weight changes, but only if taken correctly.

Gyanprakash A. Ketwaroo, MD, MSc, is an assistant professor in the division of gastroenterology and hepatology at Baylor College of Medicine, Houston, and an advanced endoscopist at the Michael E. Debakey VA Medical Center in Houston. He is an associate editor for GI & Hepatology News. He has no conflicts.

Test phagocytes to better characterize IBD dysbiosis

BY AMY KARON
MDedge News

For patients with inflammatory bowel disease, 16S ribosomal gene sequencing of lamina propria phagocytes identified microbiota closely associated with inflamed intestinal tissue, according to the results of a pilot study.

This microbiome differed from that of the intestinal mucosa, containing a markedly higher concentration of Proteobacteria, reported Rishu Dheer, PhD, of the University of Miami, and associates. The microbiota also differed between Crohn's disease and ulcerative colitis, while inflammatory gene expression did not. "The approach used in this study can narrow the spectrum of potentially dysbiotic bacterial populations" in patients with inflammatory bowel disease, the researchers wrote in Cellular and Molecular Gastroenterology and Hepatology.

Recent studies have confirmed intestinal dysbiosis in patients with inflammatory bowel disease, but little is known about disease susceptibility or severity or how microbiota correlate with inflammatory gene expression, the researchers said. They obtained ileal and colonic punch biopsy specimens from 32 patients with inflammatory bowel disease (20 with Crohn's disease and 12 with ulcerative colitis) and performed 16S ribosomal RNA sequencing of CD11+ phagocytic cells from the lamina propria. They also performed innate immune gene expression profiling. For comparison, they also studied the microbiota of the intestinal mucosa of the same patients.

Compared with mucosal microbiota, the lamina propria microbiota was enriched in Proteobacteria — the "defining phyla" associated with dysbiosis in inflammatory bowel disease, the investigators wrote. Gene profiling revealed extensive functional and metabolic differences between the lamina propria microbiota and the mucosal microbiota, regardless of whether patients had Crohn's disease or ulcerative colitis.

The microbiota associated with phagocytes was similar in inflamed and uninflamed tissue from the same patients, but it significantly differed between inflamed tissue from patients with Crohn's disease and inflamed tissue from patients with ulcerative colitis. "These results suggest that the phagocyte-associated microbiota distinguishes Crohn's disease and ulcerative colitis in the setting of inflammation," the researchers wrote.

The oncostatin M (OSM) gene, which is part of the interleukin-6 cytokine family of genes, was "highly upregulated" in inflamed CD11b+ cells from the patients, the researchers said. An adjusted analysis did not find statistically significant correlations between specific microbes and inflammatory genes, but clusters of genes were expressed at higher and lower levels in cells from inflamed versus noninflamed tissue, and these gene clusters correlated with specific bacterial genera.

"These results suggest that the variation in the abundance of specific groups of microbiota may affect gene expression levels in host lamina propria phagocyte cell types," the researchers said. They added that their study method enabled them to "amplify and detect bacteria that are found at very low abundance in the gastrointestinal tract [and that] may participate in initiating or promoting inflammatory bowel disease."

The study was supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Crohn's & Colitis Foundation of America, Micky & Madeleine Arison Family Foundation Crohn's & Colitis Discovery Laboratory, and the Martin Kaiser Chair in Gastroenterology at the University of Miami. The senior investigator disclosed ties to Prometheus, Takeda, Pfizer, AbbVie, Janssen, and several other companies. The other researchers reported having no conflicts of interest.

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SOURCE: Dheer R et al. Cell Mol Gastroenterol Hepatol. 2020. doi: 10.1016/j.jcmgh.2019.10.013.

Dysbiosis, or pathological changes in the composition or abundance of gut microbiota, has been linked to inflammatory bowel disease in multiple studies, although cause and effect relationships are sometimes difficult to establish. One issue is whether the analysis of the microbiome from stool samples or even whole colonic biopsies is the optimal method to assess its impact of altered bacterial colonization on disease, or whether it might be more informative to analyze the microbiota that are in direct contact with lamina propria phagocytes. Phagocytes, i.e. cells of the innate immune system including macrophages, monocytes, and neutrophils, are the "first responders" to bacteria that invade the ileal or colonic epithelium and thus might be a better reflection of the disease-relevant microbes than stool or whole mucosal specimens commonly analyzed.


Dr. Kaestner

Indeed, major differences between phagocyte-associated microbiota and those found in whole biopsy samples were discovered. Importantly, several of the phagocyte-associated phyla, such as Prevotella species, are known to promote Th-17-mediated mucosal inflammation. Thus, it appears that selective invasion of the mucosa by inflammation-promoting bacteria could modify the immune response and thus degrees of progression. In addition, there are striking differences between the phagocyte-associated microbiome in inflamed tissue from ulcerative colitis or Crohn's patients. Thus, for the first time it appears that microbiota are different between the two diseases in the setting of inflammation. Future research is needed to generalize these findings, and to compare the phagocyte-associated microbiome from IBD patients to that of healthy individuals.

Klaus H. Kaestner, PhD, MS, is an investigator in the department of genetics and Center for Molecular Studies in Digestive and Liver Diseases at the Perelman School of Medicine of the University of Pennsylvania in Philadelphia, codirector of Penn's Digestive Disease Research Center, and co-Editor-in-Chief of Cellular and Molecular Gastroenterology and Hepatology. He has no conflicts.

Continued from previous page

They were randomly assigned to receive thrice-daily capsules with meals consisting of PERT (40,000 FIP lipase, 25,000 FIP amylase, and 1,500 FIP protease) or placebo.

To assess adherence, the investigators had patients fill out medication diaries and counted the number of capsules left at 3-month follow-up. "Patients who took more than two-thirds of the total [PERT or placebo] dose without taking other digestive enzymes were considered to have completed the protocol," the researchers wrote.

In all, 67 patients were excluded from the intention-to-treat analysis because they withdrew consent or were lost to follow-up. Among the remaining 237 patients, PERT did not significantly outperform placebo for the primary endpoint of body weight or for secondary endpoints, including nutritional status and quality of life. The study was powered to assess the intention-to-treat population and hence missed its primary endpoint.

The per-protocol analysis included 71 patients who adhered to PERT and 93 who adhered to placebo. Among these patients, adherence to PERT versus placebo was associated with a 3.37-kg absolute mean increase in body weight ($P < .001$). The use of PERT also significantly "increased prealbumin and transferrin levels, reflecting short-term nutritional status," the researchers wrote. "However, no difference in quality of life was observed."

Subgroup analyses also favored PERT in the per-protocol analysis but not the intention-to-treat analysis, the researchers said. The use of PERT did not significantly affect the frequency of defecation in either the intention-to-treat or the per-protocol analysis.

Korea Pharmbio and the Ministry of Science and ICT provided funding. The researchers reported having no conflicts of interest.

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SOURCE: Kim H et al. Clin Gastroenterol Hepatol. 2019 Sep 12. doi: 10.1016/j.cgh.2019.08.061.

GERD symptoms affect one in three Americans

BY AMY KARON
MDedge News

For most patients, proton pump inhibitors do not control symptoms of gastroesophageal reflux disease, according to the findings of a large population-based survey study.

In all, 31% of respondents reported gastroesophageal reflux disease (GERD) symptoms within the past week, and 54% of those on proton pump inhibitors (PPIs) had breakthrough symptoms, said Sean D. Delshad, MD, MBA. In all, 54% of patients on PPIs for GERD reported having breakthrough symptoms of heartburn or regurgitation. Novel treatments are needed for patients with PPI-refractory symptoms of GERD, he and his associates wrote in Gastroenterology.

Prior population-based U.S. studies have reported a lower prevalence (16%-28%) of weekly or monthly GERD symptoms, noted Dr. Delshad of the Cedars-Sinai Center for Outcomes Research and Education in Los Angeles. However, the study cohorts do not reflect current U.S. demographics — two were 82%-90% white and the third was 43% African American. The most recent data also were collected approximately 15 years ago, the researchers noted.

For the study, they deployed a mobile app that guides users through an automated, online assessment of GI symptoms called AEGIS. Respondents were asked to select any GERD symptoms they had ever experienced and any symptoms they had experienced in the past week. Options included heartburn, acid reflux, gastroesophageal reflux, abdominal pain, bloating or gas, constipation, diarrhea, disrupted swallowing, fecal incontinence, nausea and vomiting, and "no symptoms." All 71,812 respondents were recruited by a research firm and surveyed during a 3-week period in 2015.

In all, 44% of respondents reported having ever had heartburn, acid reflux, or gastroesophageal reflux, and 31% reported having GERD symptoms in the past week. In all, 55% of respondents who had ever experienced GERD symptoms were on PPIs, 24% were on histamine$_2$ receptor blockers, and 24% were on antacid agents.

Among more than 3,000 participants on daily PPIs, 54% had persistent symptoms of GERD, which compares with the results of prior community-based studies, the investigators wrote. Current GERD symptoms and PPI-refractory GERD were especially prevalent among women, non-Hispanic whites, and individuals with comorbidities such as irritable bowel syndrome, diabetes, Crohn's disease, and endometriosis.

In an adjusted analysis, Latinos were 2.44 times more likely to have PPI-refractory GERD, compared with non-Hispanic whites. "The reason behind this finding is unclear but may be secondary to physiologic or even cultural etiologies," the researchers wrote.

The more independent and functional middle-aged and older adults are more likely to respond to online surveys. Furthermore, although incentives were used to reduce participation bias, calling the tool a "GI Survey" could have made those with GI symptoms more likely to respond. The survey ,also did not assess if respondents were taking PPIs correctly or if they had made behavioral changes to mitigate GERD.

This study was sponsored by Ironwood Pharmaceuticals, whose bile acid sequestrant IW-3718 is in late-phase development as an add-on to PPI therapy for patients with persistent GERD. Dr. Delshad reported having no relevant conflicts of interest, but two coinvestigators disclosed consulting relationships with Ironwood Pharmaceuticals.

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SOURCE: Delshad SD et al. Gastroenterology. 2019 Dec 10. doi: 10.1053/j.gastro.2019.12.014.

Heartburn is a common symptom and is ubiquitously attributed to gastroesophageal reflux disease (GERD) among patients and clinicians. However, it is important to note that, although most patients with GERD do have heartburn and/or regurgitation, many patients with these symptoms do not have GERD.


Dr. Patel

This population-based study by Delshad et al. highlights the prevalence of GERD symptoms and persistent GERD symptoms despite therapy based on a National Gastrointestinal Survey in 2015. They found that two of five participants reported GERD symptoms in the past, while one of three had symptoms in the last week. Although this highlights the high prevalence of reflux symptoms, it does not necessarily equate to a higher prevalence of GERD. This is highlighted by the fact that only 35% of patients with GERD symptoms were on therapy, suggesting that most of the patients did not find the symptoms frequent or troublesome enough to start therapy.

When the authors used a more precise definition of GERD based on the modified Montreal classification, they found that only 18% of the study population met the criteria for the disease. This is similar to prevalence of GERD reported in North America by other studies. The authors also found that, among patients on daily proton pump inhibitors (PPIs), 54% still reported persistent reflux symptoms.

Although this highlights the need for future research into developing other therapeutic modalities for GERD (such as bile-acid sequestrants), most of the patients that are "PPI refractory" have lack of response because of a functional esophageal disorder. This is highlighted by the similar risk factors for functional heartburn and the PPI-refractory group in this study: younger individuals, women, and participants with irritable bowel syndrome.

Dhyanesh A. Patel, MD, is an assistant professor of medicine at the Center for Esophageal Disorders, Vanderbilt University Medical Center, Nashville, Tenn. He has no conflicts of interest.

Belapectin misses endpoints in NASH trial

BY AMY KARON
MDedge News

For patients with nonalcoholic steatohepatitis (NASH) with cirrhosis and portal hypertension, belapectin therapy was safe but did not significantly improve fibrosis or hepatic venous pressure gradient, compared with placebo, according to the results of a multicenter phase 2b study.

After 52 weeks of infusions, the change in hepatic venous pressure gradient did not significantly differ between the 2-mg/kg group (–0.28 mm Hg) and the placebo group (0.10 mm Hg) or between the 8-mg/kg group (–0.25 mm Hg) and the placebo group (P = .1 for both comparisons). Belapectin also did not significantly improve fibrosis, nonalcoholic fatty liver disease activity score, or the frequency of various complications of cirrhosis. "However, in a subgroup analysis of patients without esophageal varices, 2 mg/kg belapectin did reduce hepatic venous pressure gradient and development of varices," wrote Naga Chalasani, MD, AGAF, of Indiana University in Indianapolis and his associates. The findings were published in Gastroenterology.

NASH leads to portal hypertension, variceal bleeding, ascites with bacterial peritonitis, hepatic encephalopathy, and liver-related death and is a leading reason for liver transplantation among women and men. Galectin-3, which is primarily secreted by macrophages, is elevated in patients with NASH and has been linked to the pathophysiology of liver fibrosis in mice. Belapectin (GR-MD-02), a complex carbohydrate that targets and disrupts galectin-3, has been found to reduce liver fibrosis and portal hypertension in rats and was safe and well tolerated in phase 1 studies.

For this double-blind trial, the researchers randomly assigned 162 patients with NASH,

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GI & HEPATOLOGY NEWS

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Protect yourself and your patients

COVID-19 *from page 1*

AGA website announcement.

In particular, the societies point out that there is recent evidence suggesting the potential for coronavirus transmission through droplets and perhaps fecal shedding, which pose potential risks in particular during endoscopy and colonoscopy procedures to other patients, endoscopy personnel, and practitioners.

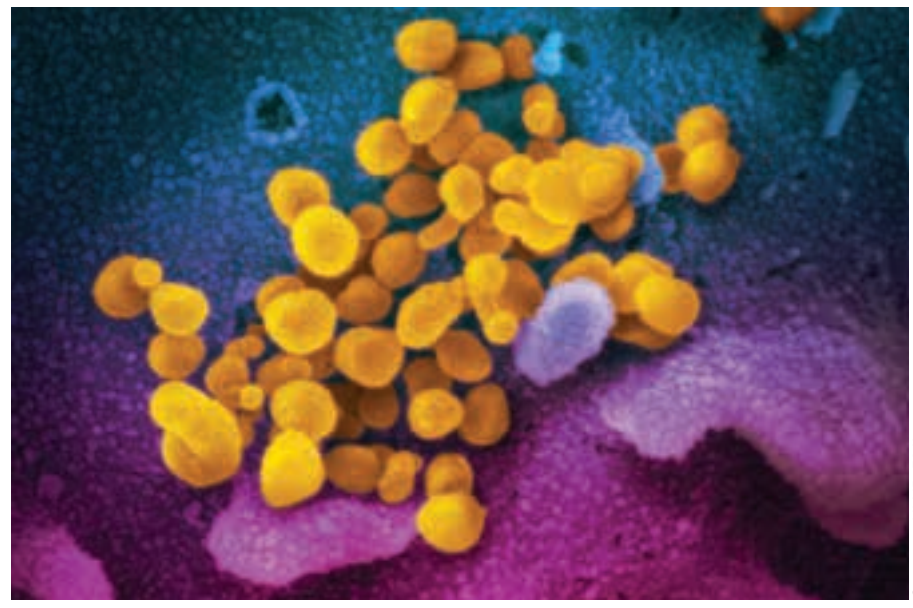
Relevant clinical factors related to COVID-19 are discussed, including the fact that asymptomatic spread can occur during the prodromal phase (the mean incubation period is approximately 5 days, with a range of 0-14 days), with viral shedding greatest when symptoms begin.

Between 20% and 30% of patients with COVID-19 infection show abnormal liver enzymes. In addition, COVID-19 patients show drops in their leukocyte counts, and elevated white blood cell counts is a poor prognostic sign, according to the release.

The Centers for Disease Control and Prevention lists vulnerable populations at the greatest risk for more serious outcomes; these include the elderly and those with severe chronic health conditions, such as heart disease, lung disease, diabetes, decompensated cirrhosis, HIV with low CD4 counts, and immunosuppression (including liver and other solid organ transplant recipients), who are at higher risk of developing more serious illness. In addition pregnancy may provide added risk.

Specific advice for the gastroenterology profession

The joint statement urges that practitioners strongly consider rescheduling elective nonurgent endoscopic procedures, although some nonurgent procedures are higher priority and may need to be performed, including cancer evaluations, prosthetic removals, and evaluation of significant symptoms. "Of note, the Surgeon General on 3/14/20 advised hospitals to postpone all elective surgeries," the document states.



COURTESY NIAID-RML

The joint statement urges that practitioners strongly consider rescheduling elective nonurgent endoscopic procedures, although some nonurgent procedures are higher priority and may need to be performed, including cancer evaluations, prosthetic removals, and evaluation of significant symptoms.

Patient concerns

In all cases, patients should be prescreened for high-risk exposure or symptoms. This includes asking about history of fever or respiratory symptoms, family members or close contacts with similar symptoms, any contact with a confirmed case of COVID-19, and recent travel to a high-risk area. "Avoid bringing patients (or their escorts) into the medical facility who are over age 65 or have one of the CDC recognized risks listed above," the societies advise.

Check body temperature of the patient upon arrival at endoscopy unit or clinic, and keep all patients at an appropriate distance from each other (6 feet is recommended) throughout the entire time in the endoscopy unit.

"For COVID-19 positive patients, or those awaiting test results, isolation precautions should be taken with procedures performed in negative pressure rooms," according to the statement.

In addition, use telemedicine where possible in elective cases, and consider phone follow-up after any procedures at 7 and 14 days to ask about new diagnosis of COVID-19 or development of its symptoms.

Those patients who are on immunosuppressive drugs for inflammatory bowel disease and autoimmune hepatitis should continue taking their medications because the risk of disease flare outweighs the chance of contracting coronavirus, according to the document. In addition, these patients should be advised to follow CDC guidelines for at-risk groups by avoiding crowds and limiting travel.

Protection of practitioners

Key factors in ensuring practitioner safety and maintaining practice functionality are discussed by the joint document. In particular, appropriate personal protective equipment (PPE) should be worn by all members of the endoscopy team: gloves, mask, eye shield/goggles, face shields, and gown, but practitioners should also be aware of how to put on and take off PPE appropriately.

"Conservation of PPE is critical. Only essential personnel should be present in cases. Consider extended use or reuse of surgical masks and eye protection in accordance with hospital policies," the document recommends.

"It is important to address our collective staff needs and institute policies that protect our workforce." To that end, the document recommends that centers should strategically assign available personnel in order to minimize concomitant exposure of those with similar or unique skill sets. This includes the use of nonphysician practitioners and fellows that cannot participate in cases for screening and triaging patients, or performing virtual visits.

Coming at a time of pandemic, when gastrointestinal symptoms have been recognized as a more common symptom of COVID-19 than previously expected and liver damage has been noted as a potential repercussion of SARS-

Continued on following page

Continued from page 10

cirrhosis, and portal hypertension (hepatic venous pressure gradient at least 6 mm Hg) to receive biweekly infusions of belapectin 2 mg/kg (54 patients), belapectin 8 mg/kg (54 patients), or placebo (54 patients). Patients were treated for 52 weeks. The primary endpoint was change from baseline in hepatic venous pressure gradient.

In a post hoc analysis of the 81 patients who had no esophageal varices at baseline, 2 mg/kg belapectin was associated with an average 1.61–mm Hg reduction in hepatic venous pressure gradient from baseline (P = .02) and with a reduction in the development of new varices (P = .03). These effects did not extend to subgroups of patients with varices at baseline, clinically significant portal hypertension, or mild portal hypertension. Moreover, 2 mg/kg belapectin did not improve fibrosis, and the higher dose of belapectin (8 mg/kg) met neither the primary endpoint nor the secondary endpoints in the overall cohort or in subgroup analyses.

"Interestingly and somewhat unexpectedly, belapectin was associated with an improvement in hepatocyte ballooning," which "is considered fundamental to the pathogenesis of disease progression in nonalcoholic steatohepatitis," the researchers wrote. "The significance of such improvement in hepatocyte ballooning in the absence of improvement of other histological components, especially inflammation, is unknown."

Galectin Therapeutics provided funding. Dr. Chalasani disclosed grant support from Galectin Therapeutics and relevant consulting relationships with NuSirt, AbbVie, Afimmune (DS Biopharma), and several other pharmaceutical companies. Sixteen coinvestigators also disclosed relationships with pharmaceutical companies, of whom eight disclosed consulting relationships, received research funding, or were employed by Galectin.

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SOURCE: Chalasani N et al. Gastroenterology. 2019 Dec 5. doi: 10.1053/j.gastro.2019.11.296.

Digestive Disease Week® 2020 is canceled

BY KARI OAKES
MDedge News

Digestive Disease Week (DDW) 2020, originally scheduled for May 2-5, 2020, in Chicago, has been canceled because of the coronavirus pandemic.

Organizers are exploring options for virtual presentation of some of the content material.

"While we are disappointed to miss the science, education, and networking that are hallmarks of DDW, we must focus on the health and safety of our community," said DDW organizers in an email notification on March 18, 2020. "Thank you for your patience as we evaluated the status of DDW in light of the rapidly changing coronavirus pandemic."

Citing the meeting's long tradition of improving patient care and the understanding of digestive diseases, the organizers promised more information to come about opportunities for remote presentation of research and educational material.

All events associated with DDW are also canceled, said the email. A page of frequently asked questions is being maintained (https://digestivediseaseweek.freshdesk.com/support/solutions/43000366101), and questions may be asked by submitting a ticket to the DDW help desk (https://digestivediseaseweek.freshdesk.com/support/tickets/new).

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Continued from previous page

CoV-2 infection, these clinical insights provide a template for gastroenterologists and related professionals for dealing with their patients and keeping themselves safe under dramatically changed circumstances.

The partnered organizations, AASLD, ACG, AGA, and ASGE, are committed to providing updated COVID-19 information as appropriate. However, "Given the evolving and fluid nature of the situation, institutions, hospitals and clinics have also been formulating their own local guidelines, so we urge you to follow the evolving CDC recommendations and your local requirements," according to the AGA website announcement.

In addition to the joint communication, the society websites each offer additional COVID-19 information. The AGA practice updates on the COVID-19 webpage provides information about announcements, such as the cancellation of Digestive Disease Week® in May, a location for AGA members to discuss their COVID-19 experiences and share advice, and links to the CDC COVID-19 updates.

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SOURCE: American Gastroenterological Association et al. 2020 Mar. COVID-19 Clinical Insights for Our Community of Gastroenterologists and Gastroenterology Care Providers.

Honoring today's luminaries in GI

The AGA Research Foundation is dedicated to supporting future leaders in GI while highlighting today's luminaries.

Our new program, AGA Honors: Celebrating Difference Makers in Our Field, recognizes individuals who have played a pivotal role in shaping the fields of gastroenterology and hepatology and supports the next generation of investigators working to advance digestive disease research and patient care.

Learn more about our honorees by visiting our website at http://foundation.gastro.org/aga-honors-celebrating/.

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Innovation in colorectal cancer screening

Disregard what is currently accepted as state of the art, reimagine the present as an imperfect stepping stone, and envision a future in which colorectal cancer (CRC) screening and surveillance are optimized. This was the direction for attendees of AGA's consensus conference – Colorectal Cancer Screening and Surveillance: Role of Emerging Technology and Innovation to Improve Outcomes.

The AGA Center for GI Innovation and Technology invited leading academic and industry experts to a working meeting to identify barriers to the optimization of CRC screening and surveillance, and to define a roadmap for overcoming these barriers.

Meeting conclusions

Although colonoscopy is widely considered to be an excellent tool for CRC screening and surveillance, barriers to optimal effectiveness exist. Barriers include lack of access to health care, financial cost, suboptimal uptake even among individuals with health insurance and financial resources, imperfect adherence to guidelines, and development of early-age, and interval cancers despite adherence to guidelines.

Novel cost-effective, sensitive, specific, and personalized strategies are needed to address these barriers.

To read about the emerging technologies discussed at the meeting, review the meeting summary in *Gastroenterology*.

ginews@gastro.org

Announcing AGA's new endoscopy journal

The recent explosion of innovations for the diagnosis and treatment of GI diseases makes it difficult to identify what will affect you today and what has implications for tomorrow.

Techniques and Innovations in Gastrointestinal Endoscopy (*TIGE*) cuts through the noise with quarterly updates featuring groundbreaking advances in GI endoscopy. Previously known as *Techniques in Gastrointestinal Endoscopy, TIGE* is the newest member of the AGA journal family and illuminates the next generation of technologies in an easily accessible, online-only format. *TIGE* will continue to be led by Co-Editors-in-Chief Vinay Chandrasekhara, MD, Mayo Clinic, Rochester, Minn., and Michael Kochman, MD, AGAF, University of Pennsylvania School of Medicine, Philadelphia, and a hand-selected editorial board of leaders in GI endoscopy.

Check out the current issue of *TIGE* focused on how lumen apposing metal stents (LAMS) are changing GI endoscopy. The issue provides a comprehensive review on the current state of LAMS and best practices for using LAMS to optimize patient outcomes.

Discover *TIGE* at tigejournal.org.

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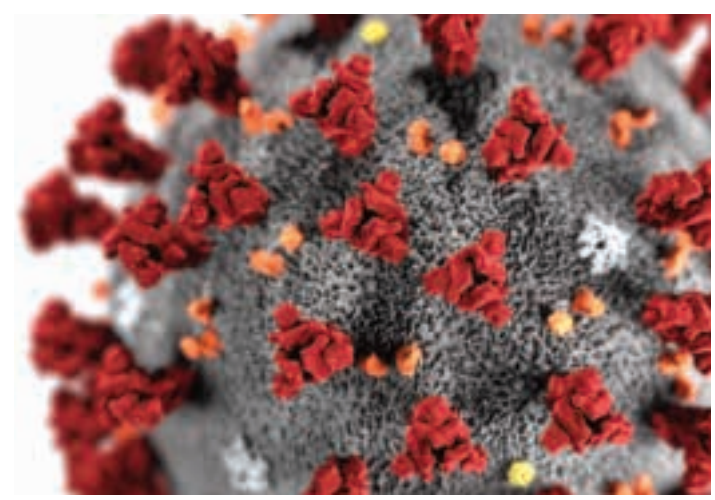
COVID-19 message from AGA

The AGA Governing Board recognizes and shares the extreme uncertainty faced by the GI community regarding the rapidly evolving coronavirus situation. Priority #1 is, as always, keeping our patients and families safe, but we also would like to ensure the safety of our GI health care providers.

COVID-19 is an emerging disease and there is more to learn about its transmission, severity, and how it will take shape in the United States. We have asked our clinical guidance experts to determine what, if any, gastroenterology-specific scientifically valid recommendations can be made. In fact, *Gastroenterology* has just published papers on GI symptoms and potential fecal transmission in coronavirus patients.

Stay tuned to www.gastro.org and your email for continued updates on coronavirus, as well as information on AGA live events given the current circumstances.

ginews@gastro.org



COURTESY CDC

The role of aspirin in the treatment of Barrett's esophagus

Should you be prescribing your Barrett's esophagus patients aspirin to prevent esophageal adenocarcinomas?

James Franklin, BMBS, and Janusz Jankowski, MD, PhD, make the case for the potential long-term chemoprevention role aspirin could play in Barrett's esophagus patients because of:

- The role of aspirin in chemoprevention of other gastrointestinal cancers especially colon.

PIXELPERFECTSTOCK/THINKSTOCK

James Franklin, BMBS, and Janusz Jankowski, MD, PhD, say aspirin could play a long-term chemoprevention role in Barrett's esophagus patients; Prasad G. Iyer, MD, MSc, AGAF, says aspirin cannot be recommended in all Barrett's patients at this time.

- Epidemiology studies showing aspirin preventing upper gastrointestinal cancer.
- Aspirin preventing inflammation and surrogate markers of risk in Barrett's esophagus.
- Aspirin preventing deaths and high-grade dysplasia in Barrett's.
- Safety of low-dose aspirin for gastrointestinal bleeding especially when given with PPIs.

Prasad G. Iyer, MD, MSc, AGAF, says aspirin cannot be recommended for chemoprevention in all Barrett's esophagus patients at this time. Specifically, in:

- Patients with Barrett's esophagus without dysplasia have low risk of progression and COX inhibition with aspirin to prevent progression is theoretically intriguing.
- Retrospective studies seem to support the potential of EAC chemoprevention with aspirin use.
- However, evidence of the efficacy of COX inhibition in prospective studies is weak. The large AspECT trial did not show evidence of reduction in the incidence of EAC or HGD with the use of 300 mg/day over a mean follow-up of almost 9 years.
- The risk of serious bleeding (gastrointestinal and cerebrovascular) is roughly doubled in patients on low-dose aspiring in large community-based primary prevention RCTs.

Review this debate and other expert discourse in AGA Perspectives, agaperspectives.gastro.org.

AGA Perspectives will soon be part of GI & Hepatology News. Same great content, new format. Stay tuned for more information.

ginews@gastro.org

AGA app improves your patient's health and bottom line

AGA has partnered with Rx-.Health, a digital health company, to create a colorectal cancer (CRC) preparatory app.

You want to find ways to improve your patient outcomes and reduce your practice costs? Now, there is an app for that. The CRC preparatory app can reduce expenses you lose from aborted or incomplete colonoscopies.

Launched in 2019, the CRC app is already generating remarkable results. The Arizona Center for Digestive Health used the CRC app and recorded a 24% improvement in bowel preparation by colonoscopy patients, a 50% reduction in aborted procedures, and a 93% patient satisfaction rate. Research conducted by Rx.Health also determined patients were using the CRC app two to four times longer than competing apps, and the CRC app was saving gastroenterologists between $20,000 and $40,000 annually.

Plans are underway between AGA and Rx.Health to expand the partnership to build apps for colorectal cancer surveillance, an inflammatory bowel disease (IBD) registry, fecal microbiota transplantation (FMT), and other GI disorders.

The CRC preparatory app can reduce expenses you lose from aborted or incomplete colonoscopies.

Interested in learning more? Visit rx.health/gi.

ginews@gastro.org

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.

Here are some recent clinical discussions in the forum regarding the coronavirus and your patients:

aga community

1. Biologic treatment for IBD in the COVID-19 era (http://ow.ly/9akD50yKW8E)

A GI colleague from Italy asks how others are managing IBD patients on ongoing biologic treatment during the coronavirus pandemic.

2. COVID-19 and colonoscopy (http://ow.ly/uYUD50yKWfS)

AGA members discuss recommendations for infection control in endoscopy centers.

3. IBD patients concerned about visiting infusion centers (http://ow.ly/gKED50yKWVZ)

How would you address patient concerns about picking up coronavirus from asymptomatic carriers at bustling infusion centers?

Join these discussions and more at https://community.gastro.org/discussions.

HBV: Rethink the free pass for immune-tolerant patients

BY M. ALEXANDER OTTO
MDedge News

MAUI, HAWAII – There might well be a cure for hepatitis B in coming years, just like there is now for hepatitis C, according to Norah Terrault, MD, chief of the division of GI and liver at the University of Southern California, Los Angeles.

"We are going to have a laundry list of new drugs" that are in the pipeline now. Phase 2 results "look encouraging. You will hear much more about this in the years ahead," said Dr. Terrault, lead author of the 2018 American Association for the Study of Liver Diseases (AASLD) hepatitis B guidance.

For now, though, the field is largely limited to the nucleoside analogues tenofovir and entecavir. Treatment is often indefinite, because although hepatitis B virus (HBV) e-antigen is cleared, it usually doesn't clear the HBV surface antigen, which is linked to liver cancer. "Even with e-antigen–negative patients, we feel that indefinite therapy is really the way to go," Dr. Terrault said at the Gastroenterology Updates, IBD, Liver Disease Conference.

One of the biggest problems with that strategy is what to do when HBV does not seem to be much of a problem for carriers. Such patients are referred to as immune tolerant.

A newly recognized cancer risk

Immune-tolerant patients tend to be young and have extremely high viral loads but no apparent ill effects, with normal ALT levels, normal histology, and no sign of cirrhosis. Although the AASLD recommends not treating these patients until they are 40 years old, waiting makes people nervous. "You have a hammer; you want to hit a nail," Dr. Terrault said.

A recent review (Gut. 2018 May;67[5]:945-52) suggests that hitting the nail might be the way to go. South Korean investigators found that 413 untreated immune-tolerant patients with a mean age of 38 years had more than twice the risk of liver cancer over 10 years than did almost 1,500 treated patients with active disease.

The study investigators concluded that "unnecessary deaths could be prevented through earlier antiviral intervention in select [immune-tolerant] patients."


Dr. Terrault

This finding is one reason "we [AASLD] are rethinking the mantra of not treating the immune tolerant. There is a group that is transitioning" to active disease. "I'm thinking we should really [lower] the age cutoff" to 30 years, as some other groups [European Association for the Study of the Liver and Asian Pacific Association for the Study of the Liver] have done, plus "patients feel really good when they know the virus is controlled, and so do physicians," Dr. Terrault said.

Entecavir versus tenofovir

Meanwhile, recent studies have raised the question of whether tenofovir is better than entecavir at preventing liver cancer.

A JAMA Oncology (2019 Jan 1;5[1]:30-6) study of some 25,000 patients in South Korea found a 32% lower risk of liver cancer when they were treated with tenofovir instead of entecavir. "This led to a lot of concern that maybe we should be moving all our patients to tenofovir," she said.

Another study, a meta-analysis published earlier this year (Hepatol Int. 2020 Jan;14[1]:105-14), confirmed the difference in cancer risk when it combined those findings with other research. After adjustment for potential confounders, including disease stage and length of follow-up, "the difference disappeared" (hazard ration, 0.87; 95% confidence interval, 0.73-1.04), authors of the meta-analysis reported.

Study patients who received entecavir tended to be "treated many years ago and tended to have more severe [baseline] disease," Dr. Terrault said.

So "while we see this difference, there's not enough data yet for us to make a recommendation for our patients to switch from" entecavir to tenofovir. "Until a randomized controlled trial is done, this may remain an issue," she said.

A question of drug holiday?

Dr. Terrault also reviewed research that suggests nucleoside analogue treatment can be stopped in e-antigen–negative patients after at least 3 years.

"The evidence is increasing that a finite NA [nucleoside analogue] treatment approach leads to higher HBsAg [hepatitis B surface antigen] loss rates, compared with the current long-term NA strategy, and can be considered a rational strategy to induce a functional cure in selected HBeAg-negative patients without cirrhosis who are willing to comply with close follow-up monitoring. ... The current observed functional cure rates" – perhaps about 40% – "would be well worth the effort," editorialists commenting on the research concluded (Hepatology. 2018 Aug;68[2]:397-400).

It's an interesting idea, Dr. Terrault said, but the virus will flare 8-12 weeks after treatment withdrawal, which is why it shouldn't be considered in patients with cirrhosis.

Dr. Terrault is a consultant for AbbVie, Merck, Gilead, and other companies and disclosed grants from those companies and others.

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HBV: Surface antigen titer and ALT predict seroconversion

BY WILL PASS
MDedge News

Among patients with hepatitis B virus (HBV) infection who are not receiving antiviral therapy, surface antigen titers and alanine aminotransferase levels may independently predict spontaneous seroconversion, based on a recent case-control study.

Patients with hepatitis B surface antigen (HBsAg) titers less than 1,000 IU/mL were significantly more likely to spontaneously seroconvert, reported principal author Sammy Saab, MD, AGAF, of the University of California, Los Angeles, and colleagues.

While the predictive value of HBsAg titers has been demonstrated for patients undergoing antiviral therapy, data are limited for spontaneous seroconversion, the investigators wrote in Journal of Clinical Gastroenterology.

To learn more about this scenario, the investigators reviewed medical records from 2,126 patients who visited a large community practice in the Los Angeles area between 2014 and 2019. Cases were defined by HBV infection with seroconversion, whereas matched controls were defined by HBV without seroconversion. A variety of demographic and clinical data were also evaluated, including age, ethnicity, sex, HBsAg titer, ALT, HBV DNA, total cholesterol, presence of fatty liver, and other factors.

The investigators identified 167 patients with HBV who were not on antiviral therapy. Of these, 14 underwent seroconversion and were matched with 70 patients who did not seroconvert. All patients were of Asian descent, most were women, and none had cirrhosis.

Across all demographic and clinical parameters, the two factors that significantly differed between cases and controls were ALT and HBsAg titer. The mean ALT for patients who seroconverted was 17.6 U/L, versus 25.1 U/L in those who did not undergo seroconversion (P less than .01). Similarly, mean titer was lower in the seroconversion group (459.8 vs. 782.0 IU/mL; P = .01).

The investigators noted that seroconversion was more common among patients with an HBsAg titer level less than 1,000 IU/mL. Specifically, 79% of patients who seroconverted had a titer less than 1,000 IU/mL, compared with just 16% of patients who did not seroconvert (P = .001).

HBV DNA levels were not predictive of seroconversion, the investigators noted, which aligns with most, but not all, previous research.

The investigators reported no disclosures.

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SOURCE: Wu CF et al. J Clin Gastroenterol. 2020 Feb 11. doi: 10.1097/MCG.0000000000001324.

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Stick with the full 12-week DAA course for acute HCV

BY M. ALEXANDER OTTO
MDedge News

The first randomized trial to see if a short course of a direct-acting antiviral works as well for acute hepatitis C virus (HCV) infection as the standard 12-week course was stopped early after it became clear that it did not, according to a report at the Conference on Retroviruses & Opportunistic Infections.

In the end, 6 weeks of sofosbuvir-velpatasvir (Epclusa) "was inferior" to 12 weeks, said investigators led by Gail Matthews, MD, PhD, an associate professor in the Viral Hepatitis Clinical Research Program at the Kirby Institute, in Sydney.

Guidelines recommend 12 weeks of direct-acting antiviral treatment, but a few observational studies have suggested that 6 weeks might be enough. Since that would make it easier for physicians and patients, and would save money, Dr. Matthews and her team set out to resolve the uncertainty with a randomized trial.

Enrollment was halted short of the 250 target because of an "unacceptably high" relapse rate of 9.7% among 93 people randomized to 6 weeks of sofosbuvir-velpatasvir versus 2% among 99 subjects randomized to the standard 12-week regimen. All the relapse patients except for one in the 12-week arm were more than 95% adherent to treatment, she said at the meeting, which was scheduled to be in Boston, but was held online this year because of concerns about spreading the COVID-19 virus.

There were 17 treatment failures (18.3%) in the short arm: two deaths, three reinfections, three lost to follow-up, and the nine relapses 12 weeks out from the end of treatment. There were eight failures (8%) in the long arm, including two reinfections, two lost to follow-up, and the two relapses, but no deaths. Excluding patients with no virologic reason for failure, Dr. Matthews said, "we see the difference in the two arms even more clearly," with viral RNA undetectable in 98% of the 12-week patients – which is in keeping with label data – versus 89% in the short arm.

Dr. Matthews said, 'we see the difference in the two arms even more clearly,' with viral RNA undetectable in 98% of the 12-week patients – which is in keeping with label data – versus 89% in the short arm.

The groups were well balanced. Almost all the subjects were men and the majority were white; the median age was 43 years. Almost two-thirds had a primary infection at baseline and HCV genotype 1 a/b was the most common in both groups. Patients had been infected for a year or less, with a median of 25 weeks.

The majority of subjects picked up the virus through homosexual sex, but about 20% by injection drug use. Over two-thirds had well-controlled HIV. There were no treatment-related discontinuations, and all the relapsed patients were successfully treated with subsequent therapy, Dr. Matthews said.

The study was conducted in the United States, Europe, Canada, New Zealand, and Australia, and funded by the National Institutes of Health. Dr. Matthews reported research grants to her institution form Abbvie and Gilead, maker of Epclusa.

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SOURCE: Matthews G. CROI 2020. Abstract 121.

Patients with COVID-19 may face risk for liver injury

BY WILL PASS
MDedge News

Patients with COVID-19 may be at risk for liver injury, but mechanisms of damage remain unclear, according to investigators.

Proposed mechanisms include direct virus-induced effects, immune-induced damage due to excessive inflammatory responses, and drug-induced injury, reported lead author Ling Xu of Huazhong University of Science and Technology, Wuhan, China, and colleagues.

"From a clinical perspective, in addition to actively dealing with the primary disease caused by coronavirus infection, attention should also be paid to monitor the occurrence of liver injury, and to the application of drugs which may induce liver damage," the investigators wrote in Liver International. "Patients with liver damage are advised to be treated with drugs that could both protect liver functions and inhibit inflammatory responses, such as ammonium glycyrrhizinate, which may, in turn, accelerate the process of disease recovery."

Liver injury appears to be significantly more common among those with severe infection. In one cohort of 82 patients who died from COVID-19, the incidence of liver injury was 78%, while another study of 36 nonsurvivors reported a rate of 58%.

The review of liver injury associated with major pathogenic coronaviruses included severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV), and the newly emergent SARS-CoV-2, which causes COVID-19.

In cases of COVID-19, reported incidence of liver injury ranges from 15% to 53%, based on elevations of alanine transaminase (ALT) and aspartate aminotransferase (AST), along with slightly elevated bilirubin levels. In severe cases, albumin decreases have also been documented.

Liver injury appears to be significantly more common among those with severe infection. In one cohort of 82 patients who died from COVID-19, the incidence of liver injury was 78%, while another study of 36 nonsurvivors reported a rate of 58%.

According to the investigators, both bile duct epithelial cells and liver cells express angiotensin-converting enzyme II (ACE2), which is an entry receptor for SARS-CoV-2; however, expression of ACE2 in bile-duct cells is "much higher" than in liver cells, and comparable with alveolar type 2 cells in the lungs.

"Bile duct epithelial cells are known to play important roles in liver regeneration and immune response," the investigators noted.

Beyond direct- and immune-induced effects of COVID-19, postmortem findings suggest that drug-induced liver injury may also be a possibility, with a number of theoretical culprits, including antibiotics, steroids, and antivirals.

Although the investigators emphasized that data are insufficient to pinpoint an exact agent, they highlighted a recent preprint study, which reported a significantly higher rate of lopinavir/ritonavir administration among patients with abnormal liver function, compared with those who had normal liver function (56.1% vs. 25%; $P = .009$).

Beyond direct- and immune-induced effects of COVID-19, postmortem findings suggest that drug-induced liver injury may also be a possibility, with a number of theoretical culprits, including antibiotics, steroids, and antivirals.

"Drug-induced liver injury during the treatment of coronavirus infection should not be ignored and needs to be carefully investigated," the investigators concluded.

Fundamental Research Funds for the Central Universities supported the work. The investigators reported no conflicts of interest.

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SOURCE: Xu L et al. Liver Int. 2020 Mar 14. doi: 10.1111/liv.14435.

FDA, FTC uniting to expand biosimilars market

BY GREGORY TWACHTMAN
MDedge News

The Food and Drug Administration is collaborating with the Federal Trade Commission (FTC) to expand the biosimilars market.

The two agencies signed a joint statement on Feb. 3, 2020, outlining four sets of goals aimed at creating meaningful competition from biosimilars against their reference biologic products.

"Competition is key for helping American patients have access to affordable medicines," FDA Commissioner Stephen Hahn, MD, said in a statement. "Strengthening efforts to curtail and discourage anticompetitive behavior is key for facilitating robust competition for patients in the biologics marketplace, including through biosimilars, bringing down the costs of these crucial products for patients."

The statement highlighted four goals. First is that the agencies will coordinate to promote greater competition in the biologic market, including the development of materials to educate the market about biosimilars. The FDA and FTC also sponsored a public workshop on March 9 to discuss competition for biologics.

The second goal has the FDA and FTC working together "to deter behavior that impedes access to samples needed for the development of biologics, including biosimilars," the joint statement notes.

Third, the agencies will crack down on "false or misleading communications about biologics, including biosimilars, within their respective authorities," according to the joint statement.

"FDA and FTC, as authorized by their respective statutes, will work together to address false or misleading communications about biologics, including biosimilars," the statement continues. "In particular, if a communication makes a false or misleading comparison between a reference product and a biosimilar in a manner that misrepresents the safety or efficacy of biosimilars, deceives consumers, or deters competition, FDA and FTC intend to take appropriate action within their respective authorities. FDA intends to take appropriate action to address such communications where those communications have the potential to impact public health."

Finally, the FTC committed to review patent settlement agreements involving biologics, including biosimilars, for antitrust violations.

Separately, the FDA issued a draft guidance document for comment on manufacturers seeking licensure of biosimilar products that do not cover all the approved uses of the reference product, as well as how to add uses over time that were not part of the initial license of the biosimilar product. The draft guidance covers licensure of products, labeling of biosimilars with fewer indications than the reference product, supplemental applications for indications not on the initial biosimilar application but covered by the reference product, and the timing of applications.

The FDA notes in the draft guidance that this is needed to cover situations such as when some indications on the reference product are covered by exclusivity, although it does encourage a biosimilar manufacturer to seek licensure for all indications that the reference product does have.

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DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz

Q1. A 25-year-old male presents to his local emergency room with malaise, nausea, vomiting, abdominal pain, and yellowish discoloration of the skin. The patient endorses having same-sex relationships for money so that he can afford to buy drugs. He has been intermittently homeless over the last year.

Vital signs are within normal limits. On examination, he has mild jaundice and no findings to suggest chronic liver disease. Liver and spleen are not enlarged.

Lab results are as follows: ALT 850 U/L, AST 700 U/L, total bilirubin 5mg/dL, direct bilirubin 3.0 mg/dL, alkaline phosphatase 137 U/L. Hepatitis A IgM positive, HBsAg negative, anti-HBc IgM negative, hepatitis C antibody negative, cytomegalovirus IgM and IgG negative, EBV viral capsid IgM negative, smooth muscle antibody+ 1:40, normal serum IgG.

Which of the following is the most likely diagnosis?
A. Autoimmune hepatitis
B. EBV
C. Hepatitis E
D. Hepatitis A

Q2. A 55-year-old female with a history of recurrent hematochezia, rectal pain, and chronic constipation presents for anorectal manometry. A recent colonoscopy was unremarkable. Perianal examination prior to the start of the manometry revealed an ulcer-like longitudinal tear at the posterior midline region of her anal canal.

Which of the following results on her anorectal manometry would most likely explain her physical examination findings?
A. Squeeze pressure of 70 mm Hg
B. Rectal contraction pressure of 50 mm Hg during strain maneuver
C. Resting pressure of 110 mm Hg
D. Expulsion of 50 mL balloon at 60 seconds
E. Relaxation of the internal anal sphincter with inflation of balloon to 30 mL in the rectum

The answers are on page 25.

Variants in NUDT15 tied to thiopurine myelosupression

BY M. ALEXANDER OTTO
MDedge News

MAUI, HAWAII – There's a new kid on the block to worry about when it comes to thiopurine pharmacogenetics: Genetic variants in the thiopurine-metabolizing enzyme nudix hydrolase 15 have been linked to a markedly increased risk of thiopurine myelosuppression among inflammatory bowel disease (IBD) patients.

The Food and Drug Administration and others already recommend screening for genetic variants in thiopurine methyltransferase (TPMT), another enzyme that metabolizes thiopurine. Polymorphisms lead to TPMT dysfunction, accumulation of cytotoxic metabolites, and increased risk of thiopurine-induced myelosuppression (TIM). Carriers are advised to use reduced doses with careful drug monitoring, or to skip thiopurines altogether.

A similar picture is emerging for nudix hydrolase 15 (NUDT15). It's been known for several years that genetic variants are not uncommon among East Asian people and lead to TIM, but their prevalence and impact among people of European decent wasn't clearly understood until now.

Investigators led by Gareth Walker, MBBS, of the Royal Devon and Exeter Hospital in Exeter, England, compared rates of problematic TPMT and NUDT15 variants among European IBD patients who had developed TIM and those who had not, about 1,000 patients in all. The majority were on azathioprine and had Crohn's disease. Finnish people were excluded because "their unique genetic background ... has led to the enrichment of some disease-causing gene variants and losses of others," according to the study, which was published in JAMA.


Dr. Loftus

Carriage of any of three coding NUDT15 variants greatly increased the risk of TIM (odds ratio, 27.3; 95% confidence interval, 9.3-116.7), independent of TPMT genotype and thiopurine dose. A particular variant – an in-frame deletion in NUDT15 – increased the risk 38-fold (95% CI, 5.1-286.1), and was carried by 5.8% of TIM patients.

The analysis also confirmed the importance of TPMT variants,

Continued on following page

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Correct answer: D

Rationale

Hepatitis A is responsible for this patient's symptoms of acute viral hepatitis with negative testing for hepatitis B and hepatitis C and positive hepatitis A IgM Ab. There has been a recent increase in hepatitis A infections. Infections in the United States occur in patients who have traveled to another country where hepatitis A virus transmission is common and in sporadic outbreaks associated with contaminated uncooked foods. An important risk group is men who have sex with men and injection drug users. A recent outbreak in Tennessee has been associated with this demographic.

Hepatitis A generally resolves over the course of weeks and does not evolve into a chronic hepatitis. However, in approximately 10% of patients or less, a relapsing course can occur. About one-fifth of these individuals will have more than one relapse. The relapse events are associated with similar symptoms that were present at the time of the initial presentation but tend to be milder. The hepatitis A IgM remains detectable in those with a relapsing course and the hepatitis A virus can be detected in the stool, indicating the possibility for infection transmission. Nearly all patients recover completely over a 6 to 12 months.

Autoimmune hepatitis is less likely with this presentation and serum IgG is normal with only weakly positive smooth muscle Ab. Hepatitis E infection would be associated with zoonotic exposure or travel to an endemic area. While EBV could be a consideration, the IgM viral capsid is negative and the pronounced transami¬nitis is more than what one would see with EBV hepatitis.

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2. https://www.tn.gov/health/cedep/tennessee-hepatitis-a-outbreak.html

Q2. Correct answer: C

Rationale

This patient's symptoms and physical examination findings suggest an anal fissure. Chronic anal fissures are believed to be caused by decreased perfusion and relative ischemia to the posterior anal sphincter. Internal anal sphincter hypertonia is thought to contribute to the reduced perfusion to the sphincter, as increased pressure on the vessels passing perpendicularly through the internal anal sphincter muscle may compromise flow. Topical smooth muscle relaxants or sphincterotomy aiming at reducing anal sphincter tone are, therefore, the major modalities of treatment for chronic anal fissure. Internal anal sphincter tone is measured on anorectal manometry by the resting anal sphincter pressure (answer C), which would be the most likely finding in this patient with anal fissure. The squeeze pressure is a measure of the contractility of the external anal sphincter (answer A). While defecatory function may also be impaired (answers B and D) in some patients with anal fissure, it is not the primary underlying pathophysiology of the injury. Patients with Hirschsprung's disease (answer E) may also develop anal fissures, but it would not be the most common finding expected in these patients.

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Continued from previous page

which were found in 30.5% of TIM patients (95/311) versus 16.4% (100/608) of patients who did not develop TIM.

"Patients with variants of either NUDT15 or TPMT, or among those with variants of both genes, had a faster onset of TIM, more severe TIM, and had a greater need for granulocyte colony–stimulating factor rescue therapy. ... Our data suggest that pretreatment sequencing of the NUDT15 gene ... may be considered prior to initiation of thiopurine therapy," the team concluded.

The prevalence of problematic NUDT15 variants among non-Finnish Europeans is about 1.6%, 6.9% among people from Finland, and almost 30% among East Asians. The team estimated NUDT15 would have to be genotyped in 95 non-Finnish Europeans to prevent one case of TIM; the number is 123 for TPMT. "Given the widespread use of thiopurines" – primarily in rheumatology and transplant medicine, in addition to gastroenterology – "these findings may have ramifications beyond the management of IBD," the investigators wrote.

"I do think it's worthwhile" to screen for NUDT15, said Edward Loftus, MD, AGAF, a professor and consultant at the Mayo Clinic in Rochester, Minn., who reviewed the study at the Gastroenterology Updates, IBD, Liver Disease Conference. "If you are a homozygote for this, your chance of getting profound leukopenia is very high, so I would probably not use a thiopurine."

"If you are going to start low dose on everyone" with careful blood monitoring, "I suppose you could just do that, but I would say if you can get" the test and "are reassured the patient is not" carrying problematic NUDT15 or TPMT variants, "then I think you just go ahead and do full dose," he said.

Testing for the relevant variants is available through the Mayo Clinic and several commercial labs.

The prevalence of problematic NUDT15 variants is 0.7% among African and 20.7% among Hispanic people.

The work was funded by the National Institutes of Health, Crohn's & Colitis UK, the Wellcome Trust, and others. Dr. Walker and other investigators reported numerous industry ties. Dr. Loftus is a consultant and/or has research funding from Abbott, Pfizer, and other companies.

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SOURCE: Walker G et al. JAMA. 2019 Feb 26;321(8):773-85.

Don't ignore early GI symptoms

GI transmission *from page 1*

dominal discomfort are less common and appear to vary between populations. The SARS coronavirus showed up in stool, even sometimes in patients discharged from the hospital. In a study of hospitalized patients in Wuhan, China, 10.1% of coronavirus patients had diarrhea and nausea in the 1-2 days before onset of fever and dyspnea. The first U.S. patient to be diagnosed had a 2-day history of nausea and vomiting, and had a loose bowel movement on the second day in the hospital. Clinicians later confirmed the presence of viral RNA in both the patient's stool and airway.

The authors say that researchers in China have isolated viral RNA from the stool of two patients (unpublished), and it has been found in saliva, suggesting the possibility of the salivary gland as an infection or transmission route.

The authors maintain that previous studies likely overlooked or neglected patients who had mild intestinal symptoms. "Many efforts should be made to be alert on the initial digestive symptoms of COVID-19 for early detection, early diagnosis, early isolation and early intervention," the authors wrote.

It appears that 2019-nCoV infects cells through an interaction between viral transmembrane spike glycoprotein (S-protein) receptor–binding domain, and the cell receptors angiotensin-converting enzyme 2 (ACE-2) and host cellular transmembrane serine protease (TMPRSS). erocytes in the ileum and colon.

The researchers call for investigation into ACE-2 fusion proteins and TMPRSS inhibitors for diagnosis, prophylaxis, or treatment of COVID-19.

The authors also noted that COVID-19 has been linked to mild to moderate liver injury as revealed by elevated aminotransferases, hypoproteinemia, and prothrombin time prolongation. SARS-associated hepatitis may be the result of viral hepatitis, immune overreaction, or a secondary effect of antiviral medications or other drugs. Little is known to date about the ability of 2019-nCoV to infect the liver, but single-cell RNA sequencing data from two distinct cohorts showed more ACE-2 expression in cholangiocytes (59.7%) than hepatocytes (2.6%).

At press time funding or financial conflicts were not available.

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E. coli strain linked with CRC mutational signature

BY WILL PASS
MDedge News

Individuals exposed to pks+ *Escherichia coli* may have an increased risk of colorectal cancer (CRC), which suggests that treating this genotoxic strain could potentially reduce risk of CRC, according to investigators.

While previous studies have demonstrated associations between various intestinal bacteria and CRC, this is the first study to show a direct link between exposure to a particular strain of bacteria and a unique mutational signature, reported lead author Cayetano Pleguezuelos-Manzano, of the Hubrecht Institute in Utrecht, Netherlands.

Recent studies showed that colibactin, a toxin produced by pks+ *E. coli*, causes a specific type of DNA damage, although the outcome of this damage remained unclear, the investigators wrote in Nature.

'This study implies that detection and removal of pks+ *E. coli,* as well as re-evaluation of probiotic strains harboring the pks island, could decrease the risk of cancer in a large group of individuals.'

To look for a possible mutational signature resulting from this damage, the investigators used human intestinal organoids, which were established from primary crypt stem cells. A pks+ *E. coli* strain was microinjected into one group of organoids, while another *E. coli* strain (pksΔclbQ), which does not produce colibactin, was injected into a second group.

Immunofluorescence showed that the organoids exposed to the pks+ *E. coli* strain developed characteristic DNA damage, whereas the control group did not.

Next, the investigators repeatedly injected organoids with either pks+ *E. coli*, pksΔclbQ, or dye only. This experiment was conducted for 5 months to achieve long-term exposure. Whole-genome sequencing showed that the pks+ *E. coli* group developed two unique mutational signatures: a single-base substitution (SBS-pks) and a small indel signature (ID-pks). Neither of the other two groups developed these signatures, which suggests that they were a direct consequence of exposure to pks+ *E. coli*.

To determine the prevalence of such mutational signatures in human patients, the investigators looked for the SBS-pks and ID-pks signatures in 5,876 human cancer genomes. One analysis involving 496 CRC metastases showed strong enrichment of both signatures, compared with other cancer types (P less than .0001). Another analysis involving 2,208 CRC tumors found that 5.0% and 4.4% of patients had SBS-pks and ID-pks enrichment, respectively.

"This study implies that detection and removal of pks+ *E. coli*, as well as re-evaluation of probiotic strains harboring the pks island, could decrease the risk of cancer in a large group of individuals," the investigators concluded.

The study was funded by the Ministry of Education, Culture and Science of the government of the Netherlands. The investigators reported additional relationships with OrigiMed, Bayer, Janssen, and others.

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SOURCE: Pleguezuelos-Manzano C et al. Nature. 2020 Feb 27. doi: 10.1038/s41586-020-2080-8.

Age divide seen in colorectal cancer screening use

BY RICHARD FRANKI
MDedge News

Roughly 79% of adults aged 65-75 years were up to date with their colorectal cancer (CRC) screening in 2018, compared with a significantly lower 63% of those aged 50-64, according to the Centers for Disease Control and Prevention.

That works out to almost 69% of Americans aged 50-75 years with up-to-date CRC screening, which was defined as a blood stool test in the past year, sigmoidoscopy in the past 5 years, and/or colonoscopy in the past 10 years, Djenaba A. Joseph, MD, and associates at the CDC's National Center for Chronic Disease Prevention and Health Promotion wrote in the Morbidity and Mortality Weekly Report.

"CRC screening has increased steadily among adults over the past 20 years," the authors noted. However, they observed a lower rate of screening in the 50-64 age group (vs. the 65-75 age group) that was consistent and significant across all demographic groups studied: sex, race/ethnicity, education, annual income, residence location, health insurance status, and regular health care provider status.

The range of screening rates in those groups went from a low of 32.6% (in 50- to 64-year-olds who had no health insurance) to a high of 87.1% (in 65- to 75-year-olds who had annual household incomes of $75,000 and over).

Up-to-date CRC screening rates were higher for the 65-75 age group in every state. The highest screening rate was observed in Rhode Island, at 84.9% in the 65-75 age group. Massachusetts had the highest rate for 50- to 64-year-olds, at 72.1%, and the highest rate for all ages studied (50-75 years), at 76.5%. Wyoming was lowest in all three categories: 51.5% in the 50-64 age group, 68.5% in the 65-75 age group, and 57.8% in the 50-75 age group.

"To achieve further increases in CRC screening to maximize benefit, specific efforts to increase screening in persons aged 50-64 years are needed," Dr. Joseph and colleagues wrote. They added that efforts might include "providing education about insurance coverage for preventive services, providing clear communication about test options, and conducting research to identify and understand barriers and facilitators to CRC screening specific to this younger age group to inform effective interventions to increase screening."

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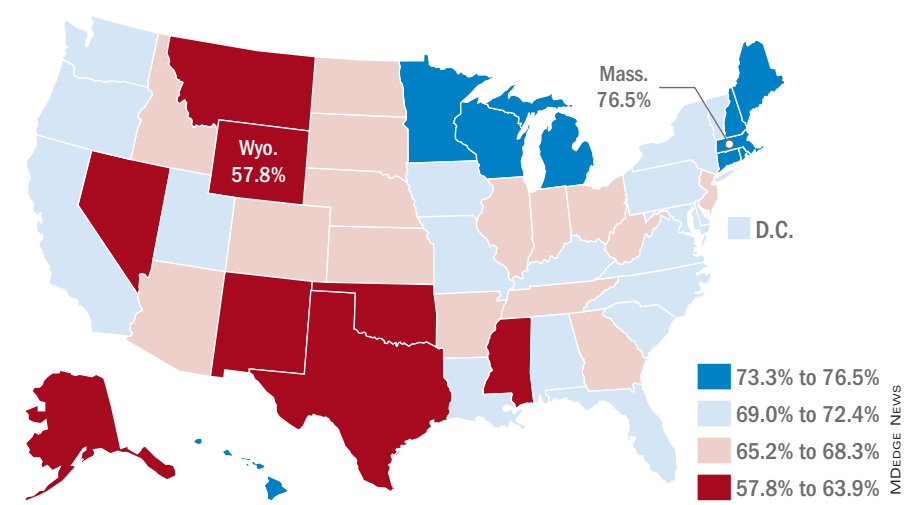
SOURCE: Joseph DA et al. MMWR. 2020 Mar 13;69(10):253-9.

Adults aged 50-75 with up-to-date colorectal cancer screening



Note: Based on data from the 2018 Behavioral Risk Factor Surveillance System survey.
Source: MMWR. 2020 Mar 13;69(10):253-9

Bariatric surgery may curtail colorectal cancer risk

BY HEIDI SPLETE
MDedge News

Bariatric surgery was associated with a significant reduction in the risk of colorectal cancer among obese adults in a retrospective study of more than 1 million individuals.

Although some studies have suggested that bariatric surgery may reduce the risk of obesity-associated cancers, such as colorectal cancer, other studies have shown an increased colorectal cancer risk after surgery, according to Laurent Bailly, MD, of Université Côte d'Azur in Nice, France, and colleagues.

In a study published in JAMA Surgery, Dr. Bailly and colleagues compared the incidence of colorectal cancer in obese patients who underwent bariatric surgery with the incidence in obese patients who did not have surgery and the incidence in the general population.

Using the French National Health Insurance Information System database, the researchers identified 1,045,348 obese adults aged 50-75 years who had no colorectal cancer at baseline. Of these patients, 74,131 underwent bariatric surgery and 971,217 did not. The mean age was 57.3 years in the surgery group and 63.4 years in the nonsurgery group.

The mean follow-up period was 6.2 years for patients who underwent adjustable gastric banding, 5.5 years for those with sleeve gastrectomy, 5.7 years for those who underwent gastric bypass, and 5.3 years for the nonsurgery group.

Results

Overall, the colorectal cancer rate was 0.6% in the surgery group and 1.3% in the nonsurgery group ($P < .001$).

The researchers calculated standardized incidence ratios (SIRs) to compare the risk of colorectal cancer in the study population with the risk among the French general population; in other words, the number of observed colorectal cancer cases divided by the number of expected cases.

In the surgery group, 423 cases of colorectal cancer were observed and 428 cases were expected, which leads to an SIR of 1.0. In the nonsurgery group, 12,629 cases were observed and 9,417 cases were expected, leading to an SIR of 1.34.

These results suggest patients in the nonsurgery group had a 34% higher risk of colorectal cancer compared with the general population, whereas the risk in the surgery group was similar to that in the general population.

Patients who underwent either gastric bypass or sleeve gastrectomy had fewer new colorectal cancer diagnoses (0.5% for both) compared with patients who had adjustable gastric banding (0.7%).

The researchers noted that this study was limited by several factors, including the retrospective, observational design and potential selection bias among surgery patients. However, the results were strengthened by the large study population and long-term follow-up.

Putting results into context

The authors of an invited commentary noted that this study is supported by results from a retrospective, U.S.-based study, which indicated that bariatric surgery has a "protective effect" against colorectal cancer (Ann Surg. 2019 Jan;269[1]:95-101).

However, these results conflict with other retrospective studies. A study of Nordic patients suggested that bariatric surgery is associated with an increased risk of colon cancer but perhaps not rectal cancer (Int J Cancer. 2019. doi: 10.1002/ijc.32770).

And a study of English patients showed an increased risk of colorectal cancer in patients who underwent gastric bypass but not in those who underwent gastric banding or sleeve gastrectomy (Br J Surg. 2018;105[12]:1650-7).

These conflicting results "imply that the jury is still out on whether bariatric surgery increases or decreases" the risk of colorectal cancer, the commentators wrote. They added that future studies "must account for differences in study population (i.e., race/ethnicity and national origin), mechanistic variation in bariatric surgical type, and length of follow-up, while also distinguishing between rectal and colon cancer before the case is settled."

This study had no outside sponsorship, and the researchers and commentators had no financial conflicts to disclose.

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SOURCES: Bailly L et al. JAMA Surg. 2020 Mar 11. doi: 10.1001/jamasurg.2020.0089; Davidson LE et al. JAMA Surg. 2020 Mar. 11. doi: 10.1001/jamasurg.2020.0090.

White House expands seniors' telehealth for COVID-19

BY GREGORY TWACHTMAN
MDedge News

The Trump Administration is looking to telehealth services to play a more prominent role in helping mitigate the spread of COVID-19 by expanding existing benefits for Medicare beneficiaries.

"Medicare can pay for office, hospital, and other visits furnished via telehealth across the country and including in patients' places of residence, starting March 6, 2020," the Centers for Medicare & Medicaid Services said in a fact sheet issued March 17.

Some of the existing benefits were previously limited to rural communities.

"These services can also be provided in a variety of settings, including nursing homes, hospital outpatient departments, and more," said CMS Administrator Seema Verma during a March 17 White House press briefing on administration actions to contain the spread of COVID-19.

That means that seniors can continue to receive their routine care without having to leave the home and risk infection, or they can get medical guidance if they have mild symptoms, which would help mitigate the spread to others.

"This shift is very important for clinicians and providers who, over the coming weeks, will face considerable strain on their time and resources," Dr. Verma said. "[It] allows the health care system to prioritize care for those who have more needs or who are in dire need, and it also preserves protective equipment."

A range of providers will be able to deliver telehealth services, including doctors, nurse practitioners, clinical psychologists, and licensed clinical social workers. Visits using telehealth services will be considered the same as in-person visits and will be paid as if the patient were seen in the office.

This expansion of Medicare telehealth services will continue for the duration of the COVID-19 public health emergency.

"In addition, the [Health & Human Services'] office of inspector general is providing flexibility for health care providers to reduce or waive cost-sharing for telehealth visits paid by federal health care programs," the fact sheet states.

Key to the expansion is that it will cover the entire United States and will not be limited to rural areas.

Dr. Verma also noted that the administration "will be temporarily suspending certain HIPAA requirements so that doctors can provide telehealth with their own phones."

She added that state Medicaid agencies can expand their telehealth services without the approval of CMS during this emergency.

AGA has released a guide to commercial telehealth COVID-19 coding policies (http://ow.ly/8CIH30qsU0B) that supplements their guide to public payors.

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Adenoma detection rate removed from 2020 MIPS, or was it?

MEGAN ADAMS, MD, JD, MSC, DAVID LEIMAN, MD, MSHP, AND SIMON MATHEWS, MD

Every year, the Centers for Medicare & Medicaid Services (CMS) releases their proposed recommendations for the next performance year and in 2019 the gastroenterology community was surprised that CMS recommended removal of QPP 0343 – Screening Colonoscopy Adenoma Detection Rate from a reportable measure in the Quality Payment Program. So what happened? Why was the measure removed from the QPP? Is there anything that we can do?

Over the next several months we will be publishing a series of articles related to the Adenoma Detection Rate Measure to give every gastroenterologist an inside look at the work that is done on your behalf and steps that you can take in the future to help your fellow gastroenterologists.

This current article explains the joint effort made by all GI societies to try to save the Adenoma Detection Rate measure from removal from the 2020 Quality Payment Program. All societies uniformly submitted a letter to CMS in disapproval of the recommendation and outlined the importance of this measure as follows:

Measure 343: Screening Colonoscopy Adenoma Detection Rate

Our societies are disappointed and disagree with CMS's decision to remove Measure 343: Screening Colonoscopy Adenoma Detection Rate (ADR) from the Quality Payment Program (QPP) beginning with the 2020 performance year.

The ADR plays a central role in quality improvement and colorectal cancer screening. We urge CMS to reconsider this decision and issue a technical correction to reinstate the measure back into the QPP, as it is the only outcome measure specific to endoscopic skills of gastroenterologists currently available for public reporting.

Studies show that high adenoma detection rates are associated with a significant reduction in colorectal cancer risk.[1] Virtually all studies on this subject have demonstrated that there is, in fact, marked variation in adenoma detection rates among physicians. Further, ADR is essential to recommended intervals[2] between screening and surveillance examinations.[2,3]

1. Variables influencing ADR. CMS explained that the measure does not account for variables that may influence the ADR such as geographic location, socioeconomic status of patient population, community compliance of screening, etc. The agency further states that, according to the risk factors outlined by the American Cancer Society, African Americans have the highest colorectal cancer incidence and mortality rates of all racial groups in the United States. "In addition, dietary factors, such as consumption of highly processed meats will contribute to an increased risk of colorectal cancer. This diet is more prevalent in lower socioeconomic areas, which could influence the outcome of the measure. There are other patient factors like education, health literacy, etc., that might also affect things like the adequacy of bowel preparation, which in turn could affect performance."

The societies advised CMS that this rationale reflects a misunderstanding of the definition of ADR, which includes all average-risk patients in whom the physician finds at least one adenoma. Further, ADR includes only colonoscopies with adequate bowel preparation and complete examinations. Studies demonstrate that ADR is not influenced by socioeconomic status and sex mix of the provider's patient population, or by the rate of screening in the community.

Socioeconomics, ethnicity, and diet are not relevant factors of ADR. That said, our societies welcome the opportunity to work with CMS on creating age- and sex-standardized ADRs for the U.S. population, if feasible, in order to capture information that CMS deems important.

2. Failure to detect all adenomas. CMS stated that the measure does not account for MIPS-eligible clinicians that fail to detect adenomas but may score higher based on the patient population.

The societies pushed back with CMS explaining that this rationale again reflects a misunderstanding of the definition of ADR, which includes average-risk patients for whom the physician finds at least one adenoma. Colonoscopy is heavily operator dependent. In an average-risk, mixed population, the variability in ADR reflects quality of the provider's endoscopic skills and pathology recognition, rather than the risk of the underlying population.

3. Incidence measure. CMS concluded that Measure 343: Screening Colonoscopy Adenoma Detection Rate is considered an "incidence measure" that does not assess the quality of the care provided. In essence, according to CMS, the measure is based on happenstance rather than the eligible clinician providing a thorough examination.

The societies strongly disagreed with this characterization of ADR. Measure 343: Screening Colonoscopy Adenoma Detection Rate is the only measure that assess the quality of the exam performed by the physician in an average-risk patient with an adequate bowel preparation. Physicians can improve their adenoma detection rate by paying attention to detail, spending more time looking for adenomas, and learning better techniques.

4. Benchmarking. CMS stated that, because of the measure construct, benchmarks calculated from this measure are misrepresented and do not align with the MIPS scoring methodology where 100% indicates better clinical care or control. Guidelines and supplemental literature support a performance target for adenoma detection rate of 25% for a mixed-sex population (20% in women and 30% in men). CMS determined that Measure 343: Screening Colonoscopy Adenoma Detection Rate may be appropriate for other programs but does not align with the scoring logic within MIPS. When this measure was introduced, according to the agency, it was under the legacy program, Physician Quality Reporting System (PQRS), a pay-for-reporting program that does not have the same scoring implications as MIPS.

This article explains the joint effort made by all GI societies to try to save the Adenoma Detection Rate measure from removal from the 2020 Quality Payment Program. All societies uniformly submitted a letter to CMS in disapproval of the recommendation and outlined the importance of this measure.

The societies reminded CMS that the 25% is the minimum requirement for performance and is not a benchmark. This minimum requirement continues to increase as well. With 25% being the threshold, for every 1% increase in ADR the risk of fatal interval colon cancer decreases by 3%. In one important study by Corley et al., the lowest quintile of ADR was 19% or lower, and was associated with the highest risk of interval colon cancer.[4]

CMS must begin to move beyond traditional approaches toward benchmarking performance where 100% compliance is expected. It was encouraging to see CMS acknowledge that nuances to evaluating scores are needed based on the ability of a measure to accurately identify and capture performance based on the patient population and measure specifications. For example, these adjustments were finalized for the blood pressure and diabetes hemoglobinA_{1c} measures, where the highest number of points will be achieved for anyone scoring 90% or higher. This modification was based on the knowledge that it is not realistic nor in the interest of patients to assume that clinicians will be able to achieve the desired targeted outcome for every patient. The potential for unintended consequences was factored into an assessment of what performance could be considered achievable.

In our view, ADR is a similar example where 100% performance across a clinician's population of patients is biologically impossible since not every individual who receives a screening colonoscopy will have an adenoma detected. ADR is the best-established colorectal neoplasia–related quality indicator and research demonstrates that high rates are associated with significant reductions in colorectal cancer risk.

CMS must continue to explore alternative strategies toward benchmarking in MIPS to ensure that achievement is fairly assessed, and top performance scores are

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determined not solely based on peer performance but also based on clinical evidence balanced with minimizing unintended consequences. The MIPS program and its benchmarking and scoring methodologies must continue to innovate to ensure that physicians provide the best possible care to their patients while also accurately and fairly representing and rewarding clinicians' performance. Continuing to promote a siloed view toward quality will only reduce the relevance of the MIPS program and lead our members to question the integrity and validity of the program.

5. Lack of alignment between cost and quality measures. CMS noted that the agency will consider the relationship between cost and quality, viewing it as an essential component of episode-based measures. Our societies agree that a value-based payment system must balance cost and quality, and as such, members of our societies have been highly engaged in the development of episode-based cost measures as part of episode group prioritization for development, CMSs' measure development contractor asked clinical subcommittee members to consider a measure's potential for alignment with established quality measures. This includes consideration of whether there is potential for overlap in covering the same patient cohort and the dimensions of care that the quality measure would be capturing in relation to a procedure or condition on which the episode-based cost measure would be focused.

The societies believe that, given the well-established role of ADR in gastroenterology practices' quality improvement programs nationwide and internationally, the introduction of the Screening/Surveillance Colonoscopy episode-based cost measure beginning in the 2019 performance year, and the proposal from CMS to introduce "MIPS Value Pathways" beginning with the 2021 performance year, the removal of Measure 343: Screening Colonoscopy Adenoma Detection Rate undermines the collective desire of CMS and our organizations to move toward aligned reporting of quality and cost measures relevant to a gastroenterologist's scope of practice and meaningful to patient care.

6. Development of a new measure. CMS suggested that there is the need for an alternative measure; however, the agency does not agree that Measure 343: Screening Colonoscopy Adenoma Detection Rate should be maintained in the interim.

Our societies welcomed the opportunity to work with CMS on developing a revised version for quality reporting purposes. We also welcomed the opportunity to suggest specific changes with CMS staff to further our shared goal on improving quality reporting and patient care. However, as of now, ADR remains the only validated, relevant, outcome-based measure to evaluate gastroenterologists' endoscopic quality. It is important that the measure be maintained in the QPP in the interim.

The societies believe the removal of Measure 343: Screening Colonoscopy Adenoma Detection Rate undermines the collective desire of CMS and our organizations to move toward aligned reporting of quality and cost measures relevant to a gastroenterologist's scope of practice and meaningful to patient care.

The importance of ADR lies in its association with long-term outcomes. Corley et al. published in the New England Journal of Medicine an examination of the association between adenoma detection rate and risks of subsequent colorectal cancer and death among 264,792 colonoscopies by 136 gastroenterologists. Patients were followed from their baseline examinations for either 10 years or until they had another colonoscopy with negative results, left the health care system, or were diagnosed with colorectal cancer. There was a 3% reduction in colorectal cancer incidence and a 5% reduction in cancer mortality for each 1% increase in adenoma detection rate. This observation remained for both proximal and distal cancer in both men and women.[4] Kaminski et al. published a study on the association between adenoma detection rate and interval cancer in Gastroenterology of 294 endoscopists and data on 146,860 colonoscopies that reviewed 895,916 person-years of follow-up evaluation through the National Cancer Registry. The study concluded that there is an association between increased adenoma detection rate and a reduced risk of interval cancer and death.[5]

The focus of any quality improvement program relative to colorectal cancer screening is to reduce colorectal cancer incidence and deaths. As discussed, the literature clearly supports driving improvement in each gastroenterologist's ADR as the mechanism to achieve these outcomes. Indeed, the first step in any gastroenterology practice's quality improvement program relative to CRC screening is to measure the endoscopist's ADR and report to it to the physician, ideally benchmarked against a group or national study. Best practice is to measure and report ADR quarterly. There are a variety of well-established and emerging techniques,[6-11] technologies,[12] and education,[13,14] with varying associated cost and effort that can be deployed as systemic interventions aimed at improving adenoma detection rate. The effect of multiple interventions over time aimed at improving ADR has demonstrated increased ADRs with notable increases in the identification of difficult to identify colorectal cancer precursors (i.e., sessile serrated adenomas) and advanced adenomas.[15] While the landscape of gastroenterology is changing, the constant is the importance of measuring an endoscopist's ADR. ADR is fundamental to training and definitions of competency for gastroenterologists.

CMS appears to have listened to the concerns brought to their attention and has been willing to have external discussions with the GI societies in an effort to placate some of these concerns. Over the next several months we will explain the current progress with CMS including reinstating a modified ADR measure as a non-MIPS measure available for reporting in a QCDR. We will also discuss what you can do as a gastroenterologist to help propel some of these efforts forward.

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