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Courtesy Dr. Alyssa M. Parian

Abigail Boateng, RN, is an infusion nurse at the infusion center in the Johns Hopkins division of gastroenterology and hepatology.

In COVID-19 era: Infusion centers shuffle services

BY DOUG BRUNK
MDedge News

It's anything but business as usual for clinicians who oversee office-based infusion centers, as they scramble to maintain services for patients considered to be at heightened risk for severe illness should they become infected with COVID-19.

"For many reasons, the guidance for patients right now is that they stay on their medications," Max I. Hamburger, MD, a managing partner at Rheumatology Associates of Long Island (N.Y.), said in an interview. "Some have decided to stop the drug, and then they call us up to tell us that they're flaring. The beginning of a flare is tiredness and other things. Now they're worried: Are they tired because of the disease, or are they tired because they have COVID-19?"

With five offices located in a region considered to be the epicenter of the COVID-19 pandemic in the United States, Dr. Hamburger and his colleagues are hypervigilant about screening patients for symptoms of

See **Infusion** · *page 20*

Liraglutide helps adolescents with obesity lose weight

BY TARA HAELLE
MDedge News

Prescribing liraglutide plus lifestyle therapy for adolescents with obesity resulted in greater weight loss and greater reduction in body mass index, compared with prescribing lifestyle therapy alone, according to findings from a new study published in the New England Journal of Medicine.

Liraglutide with lifestyle therapy also "compared favorably in terms of [body mass index] reduction," compared with other pediatric weight-management programs in the United States and with use of orlistat, wrote Aaron S. Kelly, PhD, of the University of Minnesota, Minneapolis, and colleagues. The study abstract was presented during a virtual news conference held by the Endocrine Society.

The study included adolescents aged 12-17 years, who had obesity (BMI, ≥30 kg/m^2) and had responded poorly to recommendations involving lifestyle therapy only, as judged by the site investigator and documented in the participant's medical records. The adolescents participated at one of five sites in Belgium, Mexico, Russia, Sweden, and the United States.

In the randomized, controlled, double-blind

See **Obesity** · *page 15*

COVID-19 causes financial woes for GI practices

BY ALICIA GALLEGOS
MDedge News

On a typical clinic day, Will Bulsiewicz, MD, a Charleston, S.C.–based gastroenterologist, used to see 22 patients, while other days were filled with up to 16 procedures.

Since COVID-19 however, things have vastly changed. Dr. Bulsiewicz now visits with all clinic patients through telehealth, and the volume has dipped to between zero and six patients per day. His three-doctor practice has also experienced a more than 90% reduction in endoscopy volume.

"Naturally, this has been

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INSIDE

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LETTER FROM THE EDITOR

Let's learn from our experience

COVID-19 has revealed the worst and best of our country. Some have used it to validate their racism (my Korea-born son keeps me apprised of the Asian prejudice he has experienced) and a few leaders have made policy decisions based on ideology and not science, with disastrous consequences. That said, no world threat since those 13 days in October 1962 has demonstrated so decisively our interconnectedness. The best of our country has been demonstrated by our frontline health care workers, grocery clerks, people who deliver our packages, and volunteers who help feed our fellow citizens.

Dr. Allen

We are witnessing consequences of long-term health disparities that America continues to condone. Current hotspots are clustered in cities with high population density where people (usually minorities) lack ready access to health care and live with barriers to preventive care (poor nutritional options and a lack of sufficient primary care). We have underfunded our public health system and allowed politicians to ignore science. When testing was not prioritized initially, we lost the ability to isolate and trace index cases. If we want to honor those people who have died, let's learn from our experience and change our priorities.

Private practices and health systems alike are being financially devastated. We are seeing massive numbers of people furloughed or laid off, as practices see drastic revenue loss. The transition to virtual health (video visits, remote patient monitoring) has been breathtaking with real implications about future needs for bricks and mortar. These changes in care delivery will be sustained in the future. Practice acquisitions have stopped, planned private equity exits are on hold, and the job market for graduating fellows will be challenging for the next 2 years. Now is a time for our gastroenterology societies to come together and find solutions for these problems so that our specialty can remain viable.

'Now is a time for our gastroenterology societies to come together and find solutions for these problems so that our specialty can remain viable.'

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

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 discussions addressing clinical concerns and issues arising from the COVID-19 epidemic:

1. eQ&A on recommendations for GI procedures during the COVID-19 pandemic (http://ow.ly/y1Q630qwozG) – Join guideline authors in discussing AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic, published in *Gastroenterology*.

2. IBD patients and COVID-19 (https://community.gastro.org/IBDcovid19) – To allow for timely dissemination throughout the IBD and international gastroenterology communities, members are sharing important updates regarding COVID-19 and IBD management.

3. Medicare COVID-19 changes and telehealth reimbursement (http://ow.ly/gFfT30qwps8) – Share your experiences and difficulties using telehealth platforms like Skype and facetime to connect with Medicare beneficiaries during the coronavirus epidemic.

4. Anesthesia options for in-patient endoscopy (http://ow.ly/Bl6G30qwp7E) – Colleagues examine whether intubation is the best approach for EGDs to minimize COVID-19 transmission risk.

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

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Year-long synbiotic regimen fails to improve NAFLD

BY WILL PASS
MDedge News

Synbiotics can alter gut microbiota in patients with nonalcoholic fatty liver disease (NAFLD), but associated liver benefits remain unseen, according to a recent phase 2 study.

NAFLD patients who received a year-long regimen of fructo-oligosaccharides and *Bifidobacterium animalis* had no significant changes in liver fat content or fibrosis, compared with those who received placebo, reported lead author Eleonora Scorletti, MD, of the University of Pennsylvania, Philadelphia, and colleagues.

"There is recent growing interest in the role of gut microbiota in NAFLD pathogenesis, and there are several metaorganismal pathways linking altered gut microbiota ... and NAFLD," the investigators wrote in Gastroenterology.

According to the investigators, previous studies have shown that patients with NAFLD may have some characteristic alterations to their microbiota, such as increased gram-negative bacteria or more abundant *Ruminococcus* species, the latter of which were associated with worse fibrosis.

"There is currently a lack of consistency in these findings due to the marked variance in the population studied, with differing ages, diets, and geographic locations," the investigators wrote. "Nonetheless, ... there is the possibility that manipulation of the gut microbiota to a more favorable profile could provide a beneficial effect on liver disease" in NAFLD.

To evaluate this possibility, the investigators enrolled 104 patients with NAFLD in the United Kingdom. Patients were randomly divided into a placebo (n = 49) and synbiotic group (n = 55), with the latter receiving 4 grams of fructo-oligosaccharides twice per day plus 10 billion colony-forming units of *Bifidobacterium animalis* subspecies lactis BB-12 on a daily basis. Treatments were given for 10-14 months.

Diagnostics were conducted across all participants at the beginning and end of the study: fecal microbiota analysis by 16s ribosomal DNA sequencing, liver fat measurement by proton magnetic resonance spectroscopy, biomarker-based liver fibrosis scoring, and liver stiffness assessment by vibration-controlled transient elastography.

At the end of the study, patients in the synbiotic group had increased abundance of *Bifidobacterium* and *Faecalibacterium* species and reduced proportions of *Oscillibacter* and *Alistipes* species, compared with baseline. These changes were not observed in the placebo group.

But changes in microbiota had no apparent impact on liver pathology. Although mean liver fat percentages dropped from 32.3% to 28.5% in the synbiotic group (approximately 4%), they also dropped in the placebo group, from 31.3% to 25.2% (approximately 6%), with differences between groups lacking statistical significance. Using multivariate analysis, the investigators linked these liver fat improvements, which occurred in 65% of participants, with weight loss.

"The fact that most patients had an improvement in ... liver fat, regardless of treatment allocation, is consistent with the so-called clinical trial effect, whereby participants benefit from participating in clinical trials," the investigators wrote.

Similarly to liver fat content, no significant intergroup differences were found for liver fibrosis or stiffness, whereas weight loss was linked with improvements in both disease parameters.

"Our randomized clinical trial suggests that changing the gut microbiota with this synbiotic may occur without clinically significant effects on the liver in NAFLD," they concluded.

Still, they noted that the failure of one synbiotic regimen does not discount the possibility of any microbiota-based NAFLD interventions.

"Previous studies that have tested the effects of synbiotic treatment in NAFLD have also used a combination of multiple strains of probiotics as a component of the synbiotic treatment," the investigators wrote. "Therefore, it might be possible that, because the intestine harbors trillions of bacteria, adding 1 single type of bacterium in a synbiotic may not be as effective as adding 3 or 6 different types of bacteria."

The study was supported by the National Institute of Health Research, the Parnell Diabetes Trust, and Chr. Hansen Holding. One author reported funding from Chr. Hansen unrelated to this trial.

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SOURCE: Scorletti E et al. Gastroenterology. 2020 Jan 24. doi: 10.1053/j.gastro.2020.01.031.

Biotin may benefit patients with inflammatory bowel disease

BY WILL PASS
MDedge News

Patients with inflammatory bowel disease (IBD) may benefit from biotin supplementation, according to a preclinical study.

In mice, biotin supplementation delayed onset of colitis, minimized pathology, and accelerated healing, reported lead author Jonathan Skupsky, MD, of the University of California, Irvine, and colleagues.

"Biotin deficiency often is overlooked in the setting of IBD and there have been several reports of biotin deficiency in patients with IBD," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology.

In addition to these clinical reports, Dr. Skupsky and colleagues were motivated by their previous research, which showed that, in mice, knockout of the sodium-dependent multivitamin transporter (SMVT) for intestinal biotin uptake led to intestinal inflammation and dysplasia, thereby adding evidence that IBD and biotin could be linked.

In the present study, the investigators first compared mice fed a biotin-deficient diet with those fed a biotin-rich diet. Mice lacking biotin developed alopecia and weight loss within 7 weeks and, over time, stool that was soft and bloody. At week 14, mice fed the biotin-deficient diet had intestinal inflammation, based on elevated fecal calprotectin levels. In contrast, mice fed a biotin-rich diet had no gastrointestinal pathology.

"Although no mouse model entirely recapitulates patients with IBD, this model reproduces many of the findings including weight loss, bloody diarrhea, increased fecal calprotectin, altered crypt architecture, and infiltration of neutrophils and lymphocytes to the mucosa and submucosa," the investigators wrote.

Continued on following page

Nutrient deficiency is commonly observed in patients with IBD. In fact, over half of IBD patients show deficiency in micronutrients (essential vitamins and minerals). Similarly, there are also reports of the potential negative effect of nutrient deprivation on intestinal epithelium, which could ultimately contribute to IBD. However, to date there is limited evidence supporting the notion of nutrient deficiency as a cause or an effect of IBD.

This study by Skupsky et al. highlights the role of this essential vitamin biotin in IBD pathogenesis and its potential use as a therapeutic modality in colitis. Specifically, the authors first described how biotin deficiency could lead to a colitis-like phenotype in mice and then demonstrated that deficiency of biotin was observed in a mouse model of colitis. Further, it was also shown that biotin supplementation during colitis in mice was capable of alleviating inflammation.

The authors also alluded to the potential loss of the biotin transporter, a sodium-dependent multivitamin transporter , (which was found to be down-regulated in mice with colitis, as well as in IBD patients) as one of the causative factors for biotin deficiency in IBD. However, to date, biotin deficiency has not been conclusively established in IBD patients and further systematic and well-powered studies are needed.

Dr. Dudeja

Pradeep K. Dudeja, PhD, is professor of physiology and director, divisional scholarly activities, division of gastroenterology and hepatology, department of medicine, University of Illinois at Chicago, as well as senior research career scientist, Jesse Brown VA Medical Center, Chicago. He has no conflicts.

Teens risk nutritional deficiencies after bariatric surgery

BY WILL PASS
MDedge News

Adolescents who undergo metabolic bariatric surgery may require long-term nutrient monitoring and supplementation to prevent nutritional deficiencies, according to investigators.

In a 5-year prospective study, more than a quarter of the participants who underwent vertical sleeve gastrectomy (VSG) developed two or more nutritional deficiencies, reported lead author Stavra A. Xanthakos, MD, of the Cincinnati Children's Hospital Medical Center, and colleagues.

"Although prevalence of nutritional deficiencies has been estimated largely from adult cohorts, bariatric surgery is an increasingly accepted treatment for severe obesity in youth," the investigators wrote in Clinical Gastroenterology and Hepatology. "Yet, lower adherence to supplementation and anticipated longer lifespan with altered gastrointestinal physiology may increase risk of adverse nutritional outcomes in these youth."

Previous research has suggested that teens may be at higher risk for nutritional deficiencies, but these studies were largely retrospective, or when prospective, lacked sufficient long-term follow-up, analysis of comprehensive patient factors, or inclusion of VSG, which is now the predominant technique in the field, the investigators noted.

The study involved 226 participants aged 13-19 years who underwent either Roux-en-Y gastric bypass (n = 161) or VSG (n = 67) at five tertiary-care centers in the United States during 2007-2012.

Six months after surgery, at 12 months, and on an annual basis thereafter, the investigators gathered clinical data and measured participant serum levels of ferritin; transferrin; albumin; parathyroid hormone; C-reactive protein; and vitamins A, D, B_1, B_{12}, and folate. Analyses also included sex, age, ethnicity, race, household demographics, weight, height, comorbidities, and body mass index.

The majority of participants were female (75%) and white (72%). At baseline, mean BMI and age were 52.7 kg/m^2 and 16.5 years, respectively. After 5 years, mean BMI decreased 23% without a significant difference between procedures.

Generally, nutritional deficiencies occurred earlier and were more common after gastric bypass, although both procedures were associated with increased risks.

In the gastric bypass group, 59% of participants had two or more nutritional deficiencies at 5 years, and 19% had three or more deficiencies, which represented increased rates of fivefold and sixfold, respectively, which the investigators described as "striking." In the VSG group, 27% of patients had two or more nutritional deficiencies at 5 years.

Hypoferritinemia was particularly common in both groups, with rates at year 5 of 71% and 45% among patients who underwent gastric bypass and VSG, respectively.

"Our results now provide critical evidence that VSG does in fact carry significantly lower nutritional risk than Roux-en-Y gastric bypass, but can still worsen iron status," the investigators wrote.

"Vitamin B_{12} status likewise worsened disproportionately after [gastric bypass], despite similar trajectories of weight loss after VSG," the investigators wrote. "This suggests that the differential risk is caused by anatomic and physiological differences between procedures, rather than weight loss alone."

"Our findings underscore the importance of long-term nutritional monitoring in adolescents after bariatric surgery and the need to examine impact on health outcomes," the investigators concluded.

The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Center for Advancing Translational Sciences of the National Institutes of Health. Dr. Courcoulas reported grant support from Allurion.

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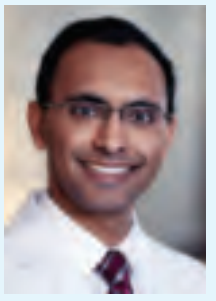
SOURCE: Xanthakos SA et al. Clin Gastro Hepatol. 2019 Nov 6. doi: 10.1016/j.cgh.2019.10.048.

The prevalence of obesity in adolescents has ballooned to about 20% of children aged 12-19 years. Prevention with diet and exercise remains the cornerstone of obesity policy in the pediatric population. Once patients develop obesity, however, bariatric surgery increasingly is being recommended as a treatment to achieve durable weight loss. Multiple large studies in adults have shown strong evidence of the efficacy of bariatric surgery; comparable data in pediatric patients have been sparse.


Dr. Abidi

The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS), a multicenter prospective consortium, was established in 2007 to better study outcomes of bariatric surgery in adolescents. Early data showed much-needed strong evidence of the safety and efficacy of metabolic and bariatric surgery in this population. The positive effects of these surgeries, however, needed to be weighed against the risk of nutritional deficiencies in this vulnerable population given their young age and poor compliance with vitamin supplementation. Early retrospective data suggested adolescents may be at higher risk of deficiencies.

The current study by Xanthakos et al. reports on 5-year prospective data from Teen-LABS specifically addressing the nutritional status of adolescents after Roux-en-Y gastric bypass and sleeve gastrectomy. Their data show deficiency only in iron and vitamin B_{12} levels after gastric bypass. More importantly, vertical sleeve gastrectomy, now the most common procedure, results in decreased risk of nutritional deficiencies compared with gastric bypass. These data add to the reassurance that surgical treatment in the adolescent population is overall safe and should be considered strongly after appropriate counseling.

Wasif M. Abidi, MD, PhD, is an assistant professor of medicine, section of gastroenterology and hepatology, Baylor College of Medicine, Houston. He has received research support from GI Dynamics.

Continued from previous page

After this experiment, another group of mice were given drinking water with 3% dextran sodium sulfate (DSS), which induced severe colitis within 7 days. The distal colons of these mice had reduced expression of SMVT, the biotin transporter. This finding was also observed in biopsy samples from patients with ulcerative colitis, suggesting a shared pathway.

"This raises the possibility that [the biotin transport pathway] could be a target for therapy," the investigators wrote.

Next the investigators tested the effect of prophylactic biotin supplementation in mice receiving 1.5% DSS in drinking water. Compared with mice that went without biotin, those that received a week of supplementation before DSS challenge had delayed, milder colitis, with histologic findings and fecal calprotectin levels that approximated those of healthy controls.

According to the investigators, these findings suggest that biotin may be able to protect against development of colitis and speed healing during early remission.

Further experiments dove deeper into cellular processes and molecular mechanisms, ultimately revealing that biotin supplementation reduced activation of NF-kappaB, which led to decreased intestinal permeability and inflammatory cytokines.

"The specific mechanism(s) linking biotin and NF-kappaB is unclear but could be mediated via the different cellular pathways that are affected by biotin availability," the investigators wrote.

They noted that IBD is a complex condition that can be difficult to accurately model; however, they also suggested that the findings are compelling enough to prompt further investigation in human patients because biotin could be a convenient therapeutic add-on.

"Biotin is available over the counter, is affordable, and it has minimal side effects, making it an ideal therapeutic if clinical trials can show similar efficacy to what we have seen in this preclinical model, the investigators wrote.

The study was funded by the Veteran's Administration and the National Institutes of Health. The investigators reported no conflicts of interest.

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SOURCE: Skupsky J et al. Cell Mol Gastroenterol Hepatol. 2019 Nov 28. doi: 10.1016/j.jcmgh.2019.11.011.

JAK inhibitors may increase risk of herpes zoster

BY WILL PASS
MDedge News

For patients with inflammatory bowel disease or other immune-mediated inflammatory diseases, Janus kinase (JAK) inhibitors appear generally safe, though they may increase the risk of herpes zoster infection, according to a large-scale systematic review and meta-analysis.

Data from more than 66,000 patients revealed no significant links between JAK inhibitors and risks of serious infections, malignancy, or major adverse cardiovascular events, reported lead author Pablo Olivera, MD, of Centro de Educación Médica e Investigación Clínica (CEMIC) in Buenos Aires and colleagues.

"To the best of our knowledge, this is the first systematic review evaluating the risk profile of JAK inhibitors in a wide spectrum of immune-mediated inflammatory diseases," they wrote in Gastroenterology.

The investigators drew studies from the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE from 1990 to 2019 and from conference databases from 2012 to 2018. Out of 973 studies identified, 82 were included in the final analysis, of which two-thirds were randomized clinical trials. In total, 101,925 subjects were included, of whom a majority had rheumatoid arthritis (n = 86,308), followed by psoriasis (n = 9,311), inflammatory bowel disease (n = 5,987), and ankylosing spondylitis (n = 319).

Meta-analysis of JAK inhibitor usage involved 66,159 patients. Four JAK inhibitors were included: tofacitinib, filgotinib, baricitinib, and upadacitinib. The primary outcomes were the incidence rates of adverse events and serious adverse events. The investigators also estimated incidence rates of herpes zoster infection, serious infections, mortality, malignancy, and major adverse cardiovascular events. These rates were compared with those of patients who received placebo or an active comparator in clinical trials.

Analysis showed that almost 9 out of 10 patients (87.16%) who were exposed to a JAK inhibitor received tofacitinib. The investigators described high variability in treatment duration and baseline characteristics of participants. Rates of adverse events and serious adverse events also fell across a broad spectrum, from 10% to 82% and from 0% to 29%, respectively.

"Most [adverse events] were mild, and included worsening of the underlying condition, probably showing lack of efficacy," the investigators wrote.

Rates of mortality and most adverse events were not significantly associated with JAK inhibitor exposure. In contrast, relative risk of herpes zoster infection was 57% higher in patients who received a JAK inhibitor than in those who received a placebo or comparator (RR, 1.57; 95% confidence interval, 1.01-2.37).

Although risks of herpes zoster may be carried across the drug class, they may not be evenly distributed given that a subgroup analysis revealed that some JAK inhibitors may bring higher risks than others; specifically, tofacitinib and baricitinib were associated with higher relative risks of herpes zoster than were upadacitinib and filgotinib.

"Although this is merely a qualitative comparison, this difference could be related to the fact that both filgotinib and upadacitinib are selective JAK1 inhibitors, whereas tofacitinib is a JAK1/JAK3 inhibitor and baricitinib a JAK1/JAK2 inhibitor," the investigators wrote. "Further studies are needed to determine if JAK isoform selectivity affects the risk of herpes zoster."

The investigators disclosed relationships with AbbVie, Pfizer, Takeda, and others.

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SOURCE: Olivera P et al. Gastroenterology. 2020 Jan 8. doi: 10.1053/j.gastro.2020.01.001.

The many different cytokines contributing to intestinal inflammation in inflammatory bowel disease patients have been a major challenge in the design of therapies. Because the JAK signaling pathway (comprised of JAK1, JAK2, JAK3, and TYK2) is required for responses to a broad range of cytokines, therapies that inhibit JAK signaling have been an active area of interest. A simultaneous and important concern, however, has been the potential for adverse consequences when inhibiting the breadth of immune and hematopoietic molecules that depend on JAK family members for their functions.


Dr. Abraham

This meta-analysis by Olivera et al. examined adverse outcomes of four different JAK inhibitors in clinical trials across four immune-mediated diseases (rheumatoid arthritis, IBD, psoriasis, and ankylosing spondylitis), finding that herpes zoster infection was significantly increased (relative risk, 1.57). In contrast, patients treated with JAK inhibitors were not at a significantly increased risk for various other adverse events.

The large number of patients represented in this meta-analysis is a major strength. Because the vast majority of placebo-controlled studies evaluated were of a relatively short duration, safety profiles will need continued assessment over longer periods.

Reduced dosing of JAK inhibitors has been a way to improve safety profiles in select immune-mediated diseases. Another approach is more selective JAK inhibition, although it is unclear whether this will eliminate the risk of herpes zoster infection. In the current meta-analysis, about 87% of the studies had evaluated tofacitinib treatment, which inhibits both JAK1 and JAK3; more selective JAK inhibitors could not be evaluated in an equivalent manner. Of note, JAK1 is required for signaling by various cytokines that participate in the response to viruses, including type I IFNs and gamma c family members (such as IL-2 and IL-15); therefore, even the more selective JAK1 inhibitors do not leave this immune function fully intact. However, simply reducing the number of JAK family members inhibited simultaneously may be sufficient to reduce risk.

JAK inhibitors warrant further evaluation as additional infectious challenges arise, particularly with respect to viruses. In addition, more selective targeting of JAK inhibition of intestinal tissues may ultimately reduce systemic effects.

Clara Abraham, MD, professor of medicine, section of digestive diseases, Yale University, New Haven, Conn., has received a research grant from Pfizer.

Genotyping improves accuracy of pancreatic cancer tests

BY WILL PASS
MDedge News

Stratifying diagnostic cutoff values of tumor markers based on genetic variants may improve detection of pancreatic cancer, according to investigators.

Stratification had the greatest positive impact on accuracy of carbohydrate antigen 19-9 (CA19-9), reported lead author Toshiya Abe, MD, PhD, of Johns Hopkins Hospital, Baltimore, and colleagues.

"Despite the evidence that genetic factors influence tumor marker levels, the potential utility of using a genetic test to improve the interpretation of tumor markers has drawn limited attention," the investigators wrote in Clinical Gastroenterology and Hepatology.

And improvements are needed, the investigators noted, particularly for early cancer detection in high-risk individuals.

"[T]he toughest hurdle for a pancreatic cancer detection blood test is the detection of stage I disease," the investigators wrote. "Cancers generally shed biomarkers in proportion to their size, and small stage I pancreatic cancers shed fewer diagnostic biomarkers into the circulation."

The control group included 504 high-risk individuals who were prospectively enrolled in the Cancer of the Pancreas Screening (CAPS) studies from 2002 to 2018, while the case group included 245 patients with pancreatic ductal adenocarcinoma (PDAC) who underwent resection at Johns Hopkins from 2010 to 2017.

The control group was randomly divided into discovery and valida-

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tion sets in order to achieve 99% specificity cutoff values, which were used to measure sensitivity in the case group. According to the investigators, high-specificity cutoff values are necessary for surveillance of asymptomatic high-risk individuals in order to minimize false-positive results.

In all patients, tumor markers and genotype were analyzed. Tumor markers included carcinoembryonic antigen (CEA), CA19-9, and cancer antigen 125 (CA-125). Genotyping included 16 single-nucleotide polymorphisms (SNPs) in 9 genes, including FUT2 and FUT3, which are known to influence levels of CA19-9.

In contrast with previous findings, which identified three relevant subgroups of FUT2/FUT3, the present study found that four distinct subgroups were significantly associated with CA19-9 levels: FUT3-null, FUT3+/-, FUT3+/+, and FUT2-null.

When CA19-9 cutoff levels were stratified by these four subgroups and applied to the 245 patients with pancreatic cancer, the investigators achieved a sensitivity of 60.8%, compared with 52.7% without stratification. The new cutoff values led to reclassification of 28 (11.4%) patients with pancreatic cancer, including 24 who switched from negative to positive, and 4 who switched from positive to negative.

In contrast with previous findings, which identified three relevant subgroups of FUT2/FUT3, the present study found that four distinct subgroups were significantly associated with CA19-9 levels: FUT3-null, FUT3+/-, FUT3+/+, and FUT2-null.

Sensitivity of the SNP-adjusted CA19-9 test was improved to 66.4% when used exclusively in patients with functional FUT3 genes. Conversely, sensitivity was markedly lower, at 36.7%, when the test was used for patients with stage I disease.

While CA19-9 testing was notably improved by SNP-based stratification, results from CEA and CA-125 testing were more modest. Standard CEA testing had a sensitivity of 13.8%, compared with 15.9% when cutoff values were stratified by FUT2 status and ABO blood group. Similarly, modifying CA-125 values based on SNPs in GAL3ST2 raised sensitivity from 15.5% to 17.6%.

Although combining SNP-modified tumor marker results did increase overall sensitivity to as high as 66.1%, this also reduced specificity to as low as 95.4%

Still, Dr. Abe and colleagues suggested that the findings demonstrate proof of concept.

The study was funded by the National Institutes of Health, Susan Wojcicki and Dennis Troper, the Pancreatic Cancer Action Network, and others. The investigators reported no conflicts of interest.

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SOURCE: Abe T et al. Clin Gastro Hepatol. 2019 Oct 29. doi: 10.1016/j.cgh.2019.10.036.

AGA issues formal recommendations for PPE during gastrointestinal procedures

Based on a review of available evidence, we have published guidance for clinicians in gastroenterology: AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic. AGA recommends increasing personal protective equipment (PPE) during all GI procedures during the coronavirus pandemic, as well as triaging procedures following a decision-making framework outlined in the recommendations document.

Review this guidance, as well as the latest AGA resources and information on coronavirus, at www.gastro.org/COVID.

Masks

1. In health care workers performing **upper GI procedures, regardless of COVID-19 status,*** AGA recommends use of N95 (or N99 or PAPR) instead of surgical masks, as part of appropriate personal protective equipment. (Strong recommendation, moderate certainty of evidence)

2. In health care workers performing **lower GI procedures regardless of COVID-19 status,*** AGA recommends the use of N95 (or N99 or PAPR) masks instead of surgical masks as part of appropriate personal protective equipment. (Strong recommendation, low certainty of evidence)

3. In health care workers performing **upper GI procedures, in known or presumptive COVID-19 patients**, AGA recommends **against** the use of surgical masks only, as part of adequate personal protective equipment. (Strong recommendation, low certainty of evidence)

Limited resource settings

4. In extreme resource-constrained settings involving health care workers performing **any GI procedures, regardless of COVID-19 status,*** AGA suggests extended use/re-use of N95 masks over surgical masks, as part of appropriate personal protective equipment. (Conditional recommendation, very low certainty of evidence)

Gloves

5. In health care workers performing **any GI procedure, regardless of COVID-19 status**, AGA recommends the use of double gloves compared with single gloves as part of appropriate personal protective equipment. (Strong recommendation, moderate certainty of evidence)

Negative pressure rooms

6. In health care workers performing **any GI procedures with known or presumptive COVID-19**, AGA suggests the use of negative pressure rooms over regular endoscopy rooms when available. (Conditional recommendation, very low certainty of evidence)

Endoscopic disinfection

7. For endoscopes utilized on patients **regardless of COVID-status**, AGA recommends continuing standard cleaning endoscopic disinfection and reprocessing protocols. (Good practice statement)

Triage

8. **All procedures should be reviewed by trained medical personnel and categorized as time-sensitive or not time-sensitive** as a framework for triaging procedures. (Good practice statement)

9. In an open access endoscopy system where the listed indication alone may provide insufficient information to make a determination about the time-sensitive nature of the procedure, **consideration should be given for the following options (i) a telephone consultation with the referring provider or (ii) a telehealth visit with the patient or (iii) a multidisciplinary team approach to facilitate decision-making for complicated patients**. (Good practice statement)

*These recommendations assume the absence of widespread reliable rapid testing for the diagnosis of COVID-19 infection or immunity.

For a detailed discussion, review the full publication in Gastroenterology.

This rapid recommendation document was commissioned and approved by the AGA Institute Clinical Guidelines Committee, AGA Institute Clinical Practice Updates Committee, and the AGA Governing Board to provide timely, methodologically rigorous guidance on a topic of high clinical importance to the AGA membership and the public. Our goal is to protect health care providers and patients from coronavirus during GI procedures.

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Congress has heard our rallying cry

AGA has advocated for provisions to protect our providers and businesses, and we're happy to report that the following provisions are in the third installation of the COVID-19 economic relief legislation.

We'll continue to push for direct funding for physicians recognizing that many practices and ASCs are struggling.

Small business relief

- Small Business Administration (SBA) loans:

  Businesses with 500 employees or fewer are eligible unless the covered industry's SBA size standard allows more than 500 employees.

  Allows 501(c)(3) nonprofits to gain access to the program.

  Increases the maximum loan amount to $10 million.

  Expands allowable uses of loans to include payroll support, such as:

  1. Paid sick or medical leave.
  2. Employee salaries.
  3. Mortgage payments.

  Provides a process for loan forgiveness for certain payroll costs as well as mortgage, rent, and utility obligations.
- Public Health and Social Services Emergency Fund:

  $100 billion for health care services related to the COVID-19.

  Reimbursement to eligible health care providers for health care–related expenses or lost revenues that are attributable to the pandemic.
- Coronavirus Economic Stabilization Act:

  $454 billion for loans, loan guarantees, and other investments for companies with losses tied to the pandemic that threaten continued operation.

Medicare provisions

- Suspension of sequestration – Physicians avoid a 2% cut in their Medicare reimbursement.
- Extension of geographic index floor – Increases Medicare payments for providers in nonurban areas.
- Increased Medicare telehealth flexibilities during the emergency period.
- AGA will continue to advocate for audio-only coverage as this issue is still not resolved.

Other key health care provisions

- Liability protections for health care professionals during the emergency response.
- Coverage of preventive services and vaccines.
- $16 billion to replenish the Strategic National Stockpile.
- $1 billion for the Defense Production Act to ensure production of personal protective equipment (PPE).

Correspondence to congressional leadership

- **March 25, 2020** – With the American Medical Association, a letter is sent requesting the inclusion of support for physician practices in any economic stimulus package.
- **March 24, 2020** – With the Alliance of Specialty Medicine, a letter is sent asking for relief for independent physicians' offices.
- **March 20, 2020** – A joint society letter is sent asking for increased funding for and access to PPE; softened prior authorization, telehealth reimbursement and Medicare reporting requirements; and financial safeguards for health care professionals and practices.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

A message from our president to the GI community

Dear colleagues,

The coronavirus pandemic has affected every facet of society, bringing almost unprecedented challenges to our world, and especially to our world of health care.

But our profession has been ignited in the way only a crisis can spark. Many of you are working on the front lines of patient care, at personal risk, lacking sufficient information and adequate resources. This is heroic work.

AGA's priority during this time of disruption is to get practical guidance into your hands to help you treat patients, and protect yourselves and your coworkers. We're also advocating on your behalf to get the resources you need and economic relief necessitated by the measures taken to fight the pandemic.

We are continually updating our COVID-19 website, www.gastro.org/covid. Check it for the latest clinical guidance, practice management information, and advocacy initiatives.

Our journals have started a collection of submissions related to COVID-19. Your AGA colleagues on the Clinical Guidelines Committee and Clinical Practice Updates Committee have been hard at work developing guidance for questions that you have asked us on Twitter, @AmerGastroAssn and the AGA Community. So join us there, where resources and insights are being shared in real time.

Your commitment to our patients is a testament to your professionalism. Our commitment at AGA is to support you.

We'll get through this together.

Hashem B. El-Serag, MD, MPH, AGAF
President,
AGA Institute

GI side effects were an issue

Obesity *from page 1*

trial, 125 participants received 3 mg liraglutide, and 126 received placebo for 56 weeks, during which both groups received lifestyle therapy, "defined as counseling about healthy nutrition and physical activity for weight loss," the authors wrote.

After 12 weeks of run-in, the treatment period lasted 56 weeks, with a follow-up 26 weeks after treatment ended. The liraglutide group retained 80.8% of its participants, and the placebo group, 79.4%.

At week 56, there were no significant differences between the groups in blood pressure, fasting lipids, fasting plasma glucose, or hemoglobin A_{1c}, the authors noted.

However, in the liraglutide group, 43.3% of participants lost at least 5% of their BMI, compared with 18.7% in the control group. Similarly, 26.1% of those in the liraglutide group had a BMI reduction of at least 10%, compared with 8.1% in the control group.

Participants in the liraglutide group also saw a greater reduction in BMI, compared with those in the placebo group (estimated difference, 4.64 percentage points), and those taking liraglutide lost 9.9 pounds (4.5 kg) more than those receiving placebo – a relative reduction of 5%. The authors noted that a weight loss of 3%-5% "significantly improves some health-related outcomes in adults."

In addition, the liraglutide group had a BMI standard-deviation score that was 0.22 lower than that in the placebo group ($P = .002$), but after the participants discontinued with the trial, "a greater increase in the BMI standard-deviation score was observed with liraglutide than with placebo (0.15)," the authors reported.

"Although evidence in children is limited, a change in BMI standard-deviation score of at least 0.20 has been suggested to be clinically meaningful," they wrote. "Some studies indicate that even temporary weight loss may have long-term benefits, but the extent to which this applies in adolescents and the extent to which long-term adherence to pharmacotherapy can be expected are unknown."

The researchers added that the reduction in standard-deviation score seen in this study, 0.22, was a bigger reduction than that seen in lifestyle therapy trials from the U.S. Preventive Services Task Force and from an overview of six Cochrane reviews. Their trial also, however, had a fairly high adherence rate, over 80%.

About twice as many participants taking liraglutide experienced gastrointestinal adverse events compared with those receiving placebo (64.8% vs. 36.5%, respectively). Those symptoms, a known side effect of this drug type, included nausea, vomiting, and diarrhea and occurred primarily during escalation of the drug dose before then dropping in frequency. Still, the authors note that the high rate of gastrointestinal effects "suggests that this treatment may not be suitable for all patients."

None of the adolescents receiving the placebo stopped treatment, but 10.4% of those taking liraglutide discontinued. One participant in the liraglutide group died by suicide, but the death was determined to be unrelated to the therapy.

Although the 0.22 reduction in the BMI standard-deviation score was for the intent-to-treat population, the authors calculated that the difference would have been 0.26 "if all participants had adhered to the treatment throughout the trial."

Novo Nordisk funded the research. Several of the authors reported that they are employees of the company.

The abstract will also be published in a special supplemental issue of the Journal of the Endocrine Society.

ginews@gastro.org

SOURCE: Kelly AS et al. NEJM. 2020 Mar 31. doi: 10.1056/NEJMoa1916038.

Cyclic vomiting syndrome: A GI primer

BY HARRISON MOOERS, MD, AND THANGAM VENKATESAN, MD

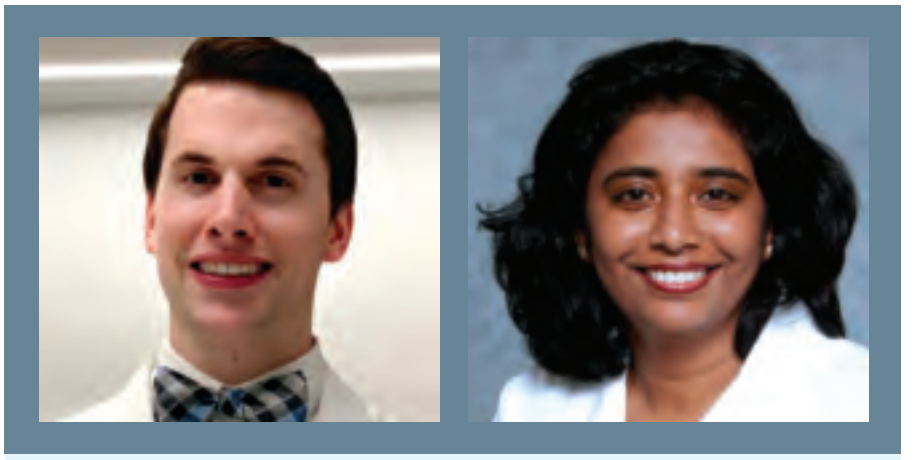
Introduction

Cyclic vomiting syndrome (CVS) is a chronic disorder of gut-brain interaction (DGBI) and is characterized by recurrent episodes of severe nausea, vomiting, and often, abdominal pain. Patients are usually asymptomatic in between episodes.[1] CVS was considered a pediatric disease but is now known to be as common in adults. The prevalence of CVS in adults was 2% in a recent population-based study.[2] Patients are predominantly white. Both males and females are affected with some studies showing a female preponderance. The mean age of onset is 5 years in children and 35 years in adults.[3]

The etiology of CVS is not known, but various hypotheses have been proposed. Zaki et al. showed that two mitochondrial DNA polymorphisms 16519T and 3010A were associated with a 17-fold increased odds of having CVS in children.[4] These polymorphisms were not associated with CVS in adults.[5] Alterations in the brain-gut axis also have been shown in CVS. Functional neuroimaging studies demonstrate that patients with CVS displayed increased connectivity between insula and salience networks with concomitant decrease in connectivity to somatosensory networks.[6] Recent data also indicate that the endocannabinoid system (ECS) and the hypothalamic-pituitary-adrenal axis are implicated in CVS with an increase in serum endocannabinoid concentration during an episode.[7] The same study also showed a significant increase in salivary cortisol in CVS patients who used cannabis. Further, single nucleotide polymorphisms (SNPs) in the gene that encodes for the cannabinoid receptor type 1 (CB1R) are implicated in CVS.[8] The CB1R is part of the ECS and is densely expressed in brain areas involved in emesis, such as the dorsal vagal complex consisting of the area postrema (AP), nucleus of the solitary tract (NTS), and also the dorsal motor nucleus of the vagus.[9] Wasilewski et al. showed an increased risk of CVS among individuals with AG and GG genotypes of CNR1 rs806380 (*P* less than .01), whereas the CC genotype of CNR1 rs806368 was associated with a decreased risk of CVS (*P* less than .05).[8] CB1R agonists – endocannabinoids and tetrahydrocannabinol (THC) – have acute antiemetic and anxiolytic effects.[9-11] The apparent paradoxical effects of cannabis in this patient population are yet to be explained and need further study.

Diagnosis and clinical features of CVS

CVS consists of four phases which include the a) prodromal phase, b) the episodic phase, c) recovery phase, and d) the interepisodic phase; and was first described by David Fleisher.[12] The phases of CVS are important for clinicians and patients alike as they have therapeutic implications.



Dr. Mooers is PGY-2, an internal medicine resident in the department of medicine, Medical College of Wisconsin, Milwaukee; **Dr. Venkatesan** is professor of medicine, division of gastroenterology and hepatology, department of medicine, Medical College of Wisconsin, Milwaukee. The authors have no conflicts to disclose.

The administration of abortive medications during a prodrome can terminate an episode. The phases of CVS are shown in Figure 1.

Most patients (~ 93%) have a prodromal phase. Symptoms during this phase can include nausea, abdominal pain, diaphoresis, fatigue, weakness, hot flashes, chills, shivering, increased thirst, loss of appetite, burping, lightheadedness, and paresthesia.[13] Some patients report a sense of impending doom and many have symptoms consistent with panic. If untreated, this progresses to the emetic phase and patients have unrelenting nausea, retching, vomiting, and other symptoms. During an episode, patients may vomit up to 20 times per hour and the episode may last several hours to days. During this phase, patients are sometimes described as being in a "conscious coma" and exhibit lethargy, listlessness, withdrawal, and sometimes disorientation.[14,15] The emetic phase is followed by the recovery phase, during which symptoms subside and patients are able to resume oral intake. Patients are usually asymptomatic between episodes but ~ 30% can have interepisodic nausea and dyspepsia. In some patients, episodes become progressively longer and the interepisodic phase is considerably shortened and patients have a "coalescence of symptoms."[12] It is important to elicit a thorough history in all patients with vomiting

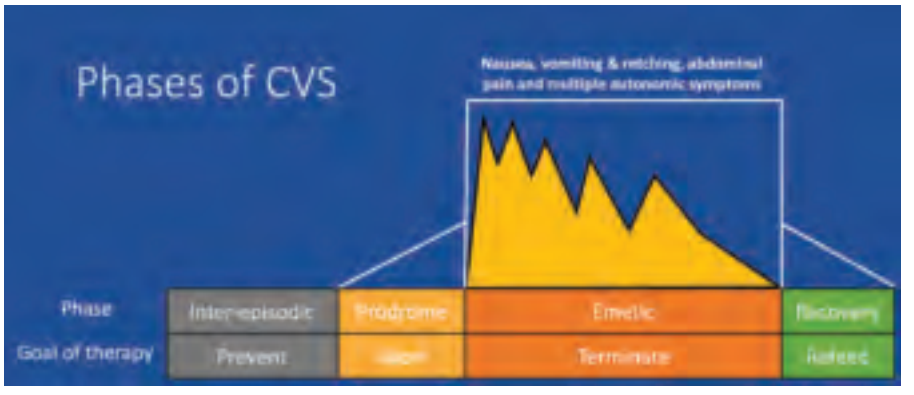


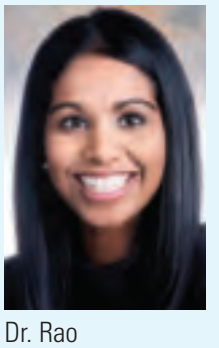
Figure 1: Phases of Cyclic Vomiting Syndrome

Adapted from Fleisher DR, Gornowicz B, Adams K, Burch R, Feldman EJ. Cyclic Vomiting Syndrome in 41 adults: The illness, the patients, and problems of management. BMC Med 2005;3:20. This work is licensed under the Creative Commons Attribution 4.0 International License https://creativecommons.org/licenses/by/4.0/, which permits unrestricted use, distribution, modification, and reproduction in any medium.

Functional gastrointestinal disorders often present a clinical challenge, both diagnostically and therapeutically, and can be frustrating for providers and patients alike. Cyclic vomiting syndrome (CVS) comprises approximately 11% of all functional gastrointestinal disorders and has become increasingly recognized among adults. CVS is characterized by recurrent episodes of nausea and vomiting with intervening asymptomatic periods. As it is a purely clinical diagnosis, it can be difficult to distinguish from other disorders with a similar constellation of symptoms.

The In Focus article for this quarter, which is brought to you by *The New Gastroenterologist*, provides an extensive review of CVS, written by Dr. Thangam Venkatesan and Dr. Harrison Mooers (Medical College of Wisconsin). This is an excellent piece which discusses the proposed pathophysiology, diagnostic criteria, phases of the disorder, and existing therapeutic options. The article lends much needed clarity to what can be a debilitating disorder and an elusive diagnosis.

Vijaya L. Rao, MD
Editor in Chief,
The New Gastroenterologist



Dr. Rao

in order to make an accurate diagnosis of CVS since coalescence of symptoms only occurs over a period of time. Episodes often are triggered by psychological stress, both positive and negative. Common triggers can include positive events such as birthdays, holidays, and negative ones like examinations, the death of a loved one, etc. Sleep deprivation and physical exhaustion also can trigger an episode.[12]

CVS remains a clinical diagnosis since there are no biomarkers. While there is a lack of data on the optimal work-up in these patients, experts recommend an upper endoscopy or upper GI series in order to rule out alternative gastric and intestinal pathology (e.g., malrotation with volvulus).[16] Of note, a gastric-emptying study is not recommended as part of the routine work-up as per recent guidelines because of the poor specificity of this test in establishing a diagnosis of CVS.[16] Biochemical testing including a complete blood count, serum electrolytes, serum glucose, liver panel, and urinalysis is also warranted. Any additional testing is indicated when clinical features suggest an alternative diagnosis. For instance, neurologic symptoms might warrant a cranial MRI to exclude an intracerebral tumor or other lesions of the brain.

The severity and unpredictable nature of symptoms makes it difficult for some patients to attend school or work; one study found that 32% of patients with CVS were completely disabled.[12] Despite increasing awareness of this disorder, patients are often misdiagnosed. The prevalence of CVS in an outpatient gastroenterology clinic in the United Kingdom was 11% and was markedly underdiagnosed in the community.[17] Only 5% of patients who were subsequently diagnosed with CVS were initially diagnosed accurately by their referring physician despite meeting criteria for the disorder.[17] A subset of patients with CVS even undergo futile surgeries.[13] Fleisher et al. noted that 30% of a 41-patient cohort underwent cholecystectomy for CVS symptoms without any improvement in disease.[12] Prompt diagnosis and appropriate therapy is essential to improve patient outcomes and improve quality of life.

CVS is associated with various comorbidities such as migraine, anxiety, depression and dysautonomia, which can further impair quality of life.[18,19] Approximately 70% of CVS patients report a personal or family history of migraine. Anxiety and depression affects nearly half of patients with CVS.[13] Cannabis use is significantly more prevalent among patients with CVS than patients with chronic vomiting.[20]

Role of cannabis in CVS

The role of cannabis in the pathogenesis of symptoms in CVS is controversial. While cannabis has antiemetic properties, there is a strong link between its use and CVS. The use of cannabis has increased over the past decade with increasing legalization.[21] Several studies have shown that 40%-80% of patients with CVS use cannabis.[22,23] Following this, cannabinoid hyperemesis syndrome (CHS) was coined as a separate entity based on this statistical association, though there are no data to support the notion that cannabis causes vomiting.[24,25] CHS has clinical features that are indistinguishable from CVS except for the chronic heavy cannabis use. A peculiar bathing behavior called "compulsive hot-water bathing" has been described and was thought to be pathognomonic of cannabis use.[26] During an episode, patients will take multiple hot showers/baths, which temporarily alleviate their symptoms. Many patients even report running out of hot water and sometimes check into a hotel for a continuous supply of hot water. A small number of patients may sustain burns from the hot-water bathing. However, studies show that this hot-water bathing behavior is also seen in about 50% of patents with CVS who do not use cannabis.[22]

CHS is now defined by Rome IV criteria, which include episodes of nausea and vomiting similar to CVS preceded by chronic, heavy cannabis use. Patients must have complete resolution of symptoms following cessation.[1] A recent systematic review of 376 cases of purported CHS showed that only 59 (15.7%) met Rome IV criteria for this disorder.[27] This is because of considerable heterogeneity in how the diagnosis of CHS was made and the lack of standard diagnostic criteria at the time. Some cases of CHS were diagnosed merely based on an association of vomiting, hot-water bathing, and cannabis use.[28] Only a minority of patients (71.19%) had a duration of follow-up more than 4 weeks, which would make it impossible to establish a diagnosis of CHS. A period of at least a year or a duration of time that spans at least three episodes is generally recommended to determine if abstinence from cannabis causes a true resolution of symptoms.[27] Whether CHS is a separate entity or a subtype of CVS remains to be determined. The paradoxical effects of cannabis may happen because of the use of highly potent cannabis products that are currently in use. A complete discussion of the role of cannabis in CVS is beyond the scope of this article, and the reader is referred to a recent systematic review and discussion.[27]

Treatment

CVS should be treated based on a biopsychosocial model with a multidisciplinary team that includes a gastroenterologist with knowledge of CVS, primary care physician, psychologist, psychiatrist, and sleep specialist if needed.[16] Initiating prophylactic treatment is based on the severity of disease. An algorithm for the treatment of CVS based on severity of symptoms is shown in Figure 2.

Patients who have mild disease (defined as fewer than four episodes/year, episodes lasting up to 2 days, quick recovery from episodes, or episodes not requiring ED care or hospitalization) are usually prescribed abortive medications.[16] These medications are best administered during the prodromal phase and can prevent progression to the emetic phase. Medications used for aborting episodes include sumatriptan (20 mg intranasal or 6 mg subcutaneous), ondansetron (8 mg sublingual), and diphenhydramine (25-50 mg).[30,31]

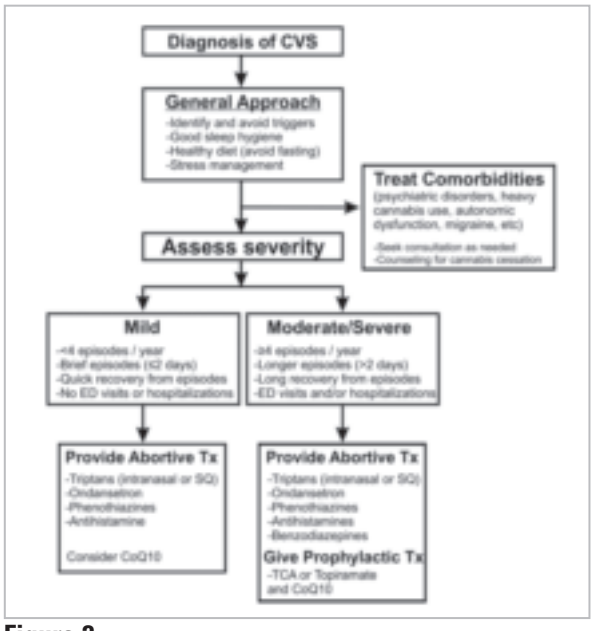


Figure 2.

Adapted and reprinted by permission from the Licensor: Springer Nature, Current Treatment Options in Gastroenterology, Bhandari S, Venkatesan T. Novel Treatments for Cyclic Vomiting Syndrome: Beyond Ondansetron and Amitriptyline, 14:495-506, Copyright 2016.

This combination can help abort symptoms and potentially avoid ED visits or hospitalizations. Patients with moderate-to-severe CVS are offered prophylactic therapy in addition to abortive therapy.[16]

Recent guidelines recommend tricyclic antidepressants (TCAs) as the first-line agent in the prophylaxis of CVS episodes. Data from 14 studies determined that 70% (413/600) of patients responded partially or completely to TCAs.[16] An open-label study of 46 patients by Hejazi et al. noted a decline in the number of CVS episodes from 17 to 3, in the duration of a CVS episode from 6 to 2 days, and in the number of ED visits/ hospitalizations from 15 to 3.3.[32] Amitriptyline should be started at 25 mg at night and titrated up by 10-25 mg each week to minimize emergence of side effects. The mean effective dose is 75-100 mg or 1.0-1.5 mg/kg. An EKG should be checked at baseline and during titration to monitor the QT interval. Unfortunately, side effects from TCAs are quite common and include cognitive impairment, drowsiness, dryness of mouth, weight gain, constipation, and mood changes, which may warrant dose reduction or discontinuation. Antiepileptics such as topiramate, mitochondrial supplements such as Coenzyme Q10 and riboflavin are alternative prophylactic agents in CVS.[33] Aprepitant, a newer NK1 receptor antagonist

Continued on following page

Table 1. Rome IV criteria for cyclic vomiting syndrome[1]

Must include all of the following:
Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)
▶ At least three discrete episodes in the prior year and two episodes in the past 6 months, occurring at least 1 week apart
▶ Absence of vomiting between episodes, but other milder symptoms can be present between cycles
▶ Supportive criteria: Personal or family history of migraine headaches

MDEDGE NEWS

Source: Adapted from Stanghellini V, Talley NJ, Chan F et al. Gastroduodenal Disorders. Gastroenterology. 2016;150(6):1380-92. Used with permission of Elsevier.

AGA Guideline: Management of eosinophilic esophagitis

BY AMY KARON
MDedge News

Patients with eosinophilic esophagitis should receive topical steroids instead of oral steroids or no treatment, according to new recommendations from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters.

In a pooled analysis of eight double-blind clinical trials, monotherapy with topical budesonide or topical fluticasone was about 61% more likely than placebo to produce histologic remissions in patients with eosinophilic esophagitis (relative risk of failure to achieve remission, 0.39; 95% confidence interval, 0.26-0.58), wrote Ikuo Hirano, MD, of Northwestern University, Chicago. Although these trials differed methodologically, the results were robust enough to warrant a strong recommendation for topical steroids, wrote Dr. Hirano and coauthors of the guidelines, published in Gastroenterology (doi: 10.1053/j.gastro.2020.02.038). "[T]he same inhaled steroid agents are considered very safe for use in children and adults with asthma and are routinely used in [its] primary management," they noted.

All other recommendations in the guidelines are graded as conditional, reflecting a lack of high-quality supporting evidence. For example, only one study to date has compared topical and oral steroids for patients with eosinophilic esophagitis. In this pediatric trial, children benefited similarly from fluticasone (two puffs four times daily) and oral prednisone (1 mg/kg twice daily), but prednisone caused side effects (weight gain and cushingoid appearance) in 40%


Dr. Hirano

Continued on page 20

Continued from previous page

has been found to be effective in refractory CVS.[34] In addition to pharmacotherapy, addressing comorbid conditions such as anxiety and depression and counseling patients to abstain from heavy cannabis use is also important to achieve good health care outcomes.

In summary, CVS is a common, chronic disorder of gut-brain interaction with episodic nausea, vomiting, and often, abdominal pain. Symptoms can be disabling, and prompt diagnosis and therapy is important. CVS is associated with multiple comorbid conditions such as migraine, anxiety and depression, and a biopsychosocial model of care is essential. Medications such as amitriptyline are effective in the prophylaxis of CVS, but side effects hamper their use. Recent recommendations for management of CVS have been published.[16] Cannabis is frequently used by patients for symptom relief but use of high-potency products may cause worsening of symptoms or unmask symptoms in genetically predisposed individuals.[23] Studies to elucidate the pathophysiology of CVS should help in the development of better therapies.

See references at MDedge.com/gihepnews/new-gastroenterologist.

Gastroenterology

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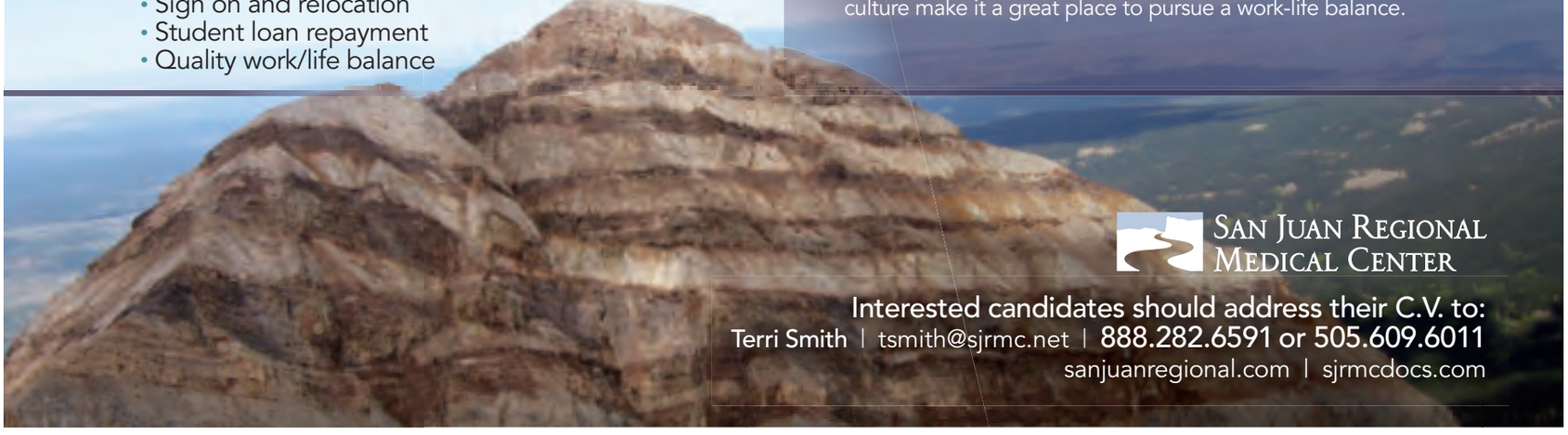

San Juan Regional Medical Center

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Safety comes first

Infusion *from page 1*

the virus before they visit one of the three practice locations that provide infusion services. This starts with an automated phone system that reminds patients of their appointment time. "Part of that robocall now has some questions like, 'Do you have any symptoms of COVID-19?' 'Are you running a fever?' " The infusion nurses are also calling the patients in advance of their appointment to check on their status. "When they get to the office location, we ask them again about their general health and check their temperature," said Dr. Hamburger. "We're doing everything we can to talk to them about their own state of health and to question them about what I call extended paranoia: like, 'Who are you living with?' 'Who are you hanging out with?'... We do everything we can to see if there's anybody who might have had the slightest [contact with someone who has COVID-19]. Because if I lose my infusion nurse, then I'm up the creek."

Dr. Hamburger

The infusion nurse wears scrubs, a face mask, and latex gloves. She and her staff are using hand sanitizer and cleaning infusion equipment with sanitizing wipes as one might do in a surgical setting. "Every surface is wiped down between patients, and the nurse is changing gloves between patients," said Dr. Hamburger, who was founding president of the New York State Rheumatology Society before retiring from that post in 2017. "Getting masks has been tough. We're doing the best we can there. We're not gloving patients but we're masking patients."

As noted in guidance from the American College of Rheumatology and other medical organizations, following the Center for Disease Control and Prevention's recommendation to stay at home during the pandemic has jump-started conversations between physicians and their patients about modifying the time interval between infusions. "If they have been doing well for the last 9 months, we're having a conversation such as 'Maybe instead of getting your Orencia every 4 weeks, maybe we'll push it out to 5 weeks, or maybe we'll push the Enbrel out to 10 days and the Humira out 3 weeks, et cetera," Dr. Hamburger said. "One has to be very careful about when you do that, because you don't want the patient to flare up because it's hard to get them in, but it is a natural opportunity to look at this. We're seeing how we can optimize the dose, but I don't want to send the message that we're doing this because it changes the patient's outcome, because there's zero evidence that it's a good thing to do in terms of resistance."

'We do everything we can to see if there's anybody who might have had the slightest [contact with someone who has COVID-19]. Because if I lose my infusion nurse, then I'm up the creek.'

At the infusion centers operated by the Johns Hopkins division of gastroenterology and hepatology, Baltimore, clinicians are not increasing the time interval between infusions for patients at this time. "We're keeping them as they are, to prevent any flare-ups. Our main goal is to keep patients in remission and out of the hospital,"

'We are trying to maintain a "COVID-free zone." Therefore, no physicians who have served in a hospital ward are allowed in the infusion suite because we don't want any carriers of COVID-19. Same with the nurses.'

said Alyssa M. Parian, MD, medical director of the infusion center and associate director of the university's GI department. "With Remicade specifically, there's also the risk of developing antibodies if you delay treatment, so we're basically keeping everyone on track. We're not recommending a switch from infusions to injectables, and we also are not speeding up infusions, either. Before this pandemic happened, we had already tried to decrease all Remicade infusions from 2 hours to 1 hour for patient satisfaction. The Entyvio is a pretty quick, 30-minute infusion."

To accommodate patients during this era of physical distancing measures recommended by the CDC, Dr. Parian and her infusion nurse manager Elisheva Weiser converted one of their two outpatient GI centers into an infusion-only suite with 12 individual clinic rooms. As soon as patients exit the second-floor elevator, they encounter a workstation prior to entering the office where they are screened for COVID-19 symptoms and their temperature is taken. "If any symptoms or temperature comes back positive, we're asking them to postpone their treatment and consider COVID testing," she said.

Instead of one nurse looking after four patients in one room during infusion therapy, now one nurse looks after two patients who are in rooms next to each other. All patients and all staff wear masks while in the center. "We always have physician oversight at our infusion centers," Dr. Parian said. "We are trying to maintain a 'COVID-free zone.' Therefore, no physicians who have served in a hospital ward are allowed in the infusion suite because we don't want any carriers of COVID-19. Same with the nurses. Additionally, we limit the staff within the suite to only those who are essential and don't allow anyone to perform telemedicine or urgent clinic visits in this location. Our infusion center staff are on a strict protocol to not come in with any symptoms at all. They are asked to take their temperature before coming in to work."

Dr. Parian

She and her colleagues drew from recommendations from the joint GI society message on COVID-19, the Crohn's and Colitis Foundation, and the International Organization for the Study of Inflammatory Bowel Disease to inform their approach in serving patients during this unprecedented time. "We went as conservative as possible because these are immunosuppressed patients," she said. One patient on her panel who receives an infusion every 8 weeks tested positive for COVID-19 between infusions, but was not hospitalized. Dr. Parian said that person will be treated only 14 days after the all symptoms disappear. "That person will wear a mask and will be infused in a separate room," she said.

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of patients, while topical steroids caused oral candidiasis (thrush) in only 15% of patients. Similarities between pediatric and adult eosinophilic esophagitis support the use of topical versus oral steroids in both groups, the guidelines conclude.

Eosinophilic esophagitis tends to be chronic and can progress to recurrent dysphagia, esophageal impactions, and stricture if left untreated. For this reason, the guidelines call for remitted patients to stay on topical steroids as maintenance therapy despite "very low confidence in the estimated benefits of [any type of] long-term therapy." In a very small trial, 1 year of low-dose budesonide maintenance therapy (0.25 mg twice daily) outperformed placebo, but only 36% of patients maintained less than 5 eosinophils per high-power field. Other studies have produced mixed results. Pending more data, the guidelines call maintenance treatment with topical steroids, proton pump inhibitors, and elimination diets "reasonable options" that comprise "a preference-sensitive area of management."

Dietary interventions for eosinophilic esophagitis include the elemental diet (amino acid–based formulas), the empiric six-food elimination diet, and eliminating foods based on allergy testing. The guidelines cite moderate-quality evidence for the elemental diet, which induced histologic remissions (less than than 15 eosinophils per high-power field) in nearly 94% of patients in six single-arm observational studies (in contrast, the rate of histologic failure with placebo is nearly 87%). However, patients may struggle to adhere to both the elemental diet and the six-food elimination diet, which has less supporting evidence. Hence, patients "may reasonably decline" these treatment options and "may prefer alternative medical or di-

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Elective procedures have come to a halt

Financial *from page 1*

devastating," Dr. Bulsiewicz said in an interview. "Our practice was started in 1984, and we had a business model that we used for the history of our practice. That practice model was upended in a matter of 2 weeks."

Dr. Bulsiewicz is far from alone. Community GI practices across the country are experiencing similar financial distress in the face of COVID-19. In addition to a decrease in patient referrals, the Centers for Medicare & Medicaid Services has requested that all elective esophagogastroduodenoscopies, colonoscopies, endoscopies, surgeries, and procedures be delayed during the coronavirus outbreak to conserve critical equipment and limit virus exposure. The guidance aligns with recent recommendations issued by American Gastroenterological Association, American Association for the Study of Liver Diseases, American College of Gastroenterology, and American Society for Gastrointestinal Endoscopy. The lack of patients has led to plummeting revenue for many GI practices and resulted in layoffs, reduced hours, and limited salaries in order to keep practices afloat.

Dr. Jain

"We've had to make drastic changes in the way we work," said Rajeev Jain, MD, AGAF, a Dallas-based gastroenterologist. "The way private practices are economically set up, they don't have large reserves of capital or liquidity. We're not like Apple or these big companies that have these massive cushions. It's one thing when you have a downturn in the economy and less people come to get care, but when you have a complete shutdown, your revenue stream to pay your bills is literally dried up."

Dr. Jain's practice is part of Texas Digestive Disease Consultants (TDDC), which provides GI care for patients in Texas and Louisiana. TDDC is part of GI Alliance, a private equity–based consolidation of practices that includes several states and more than 350 GIs. The management services organization is a collaboration between the private equity firm and the partner physicians. Since the COVID-19 outbreak, Dr. Jain said his practice has seen a dramatic drop in patients. Normally, Dr. Jain would perform between 25 and 30 outpatient scopes over the course of 2 days, he said. On a recent Monday, he performed two procedures. To preserve cash flow, Dr. Jain said he and his senior partners are not taking an income right now. Some employees were recently furloughed and laid off.

Dr. Jain said his practice has seen a dramatic drop in patients. Normally, he would perform between 25 and 30 outpatient scopes over the course of 2 days, he said. On a recent Monday, he performed two procedures. To preserve cash flow, Dr. Jain said he and his senior partners are not taking an income right now.

"I never in my life thought that I would have to lay off people because of an economic issue," Dr. Jain said. "That's psychological strain that as a physician owner you feel because these are people that you work with on a day-to-day basis and you don't want them suffering either. That's been a tough thing."

James S. Leavitt, MD, said his 17-physician center in Miami has furloughed about half its staff. The center is part of Gastro Health, a private equity firm–based medical group with more than 250 providers in four states. Dr. Leavitt, president and chief clinical officer for Gastro Health, said his center has gone from about 150 patients per day to 5 or fewer, while procedures have dropped from more than 100 a day to maybe 5.

Having partnered with a PE firm however, Dr. Leavitt believes his practice is bettered situated to manage the health crisis and address financial challenges.

"It's made us better prepared to weather the storm. We have a very high-powered, sophisticated administration and much broader base and access to capital. [For example], we had a lot of depth in management so that we could roll out a robust televisit program in a week in four states with over 250 doctors."

From a business standpoint however, certain goals for the company are on hold, he said, such as closing on potential acquisitions.

Telemedicine works well for many patients, particularly for follow-up patients and for patients who have an established relationship with Dr. Leavitt, he said. There are limitations of course, he noted.

"If I were a dermatologist, maybe I could see the skin rash, but you can't examine the patient," he said. "There are certain things you can't do. If a patient has significant abdominal pain, a televisit isn't the greatest."

That's why Dr. Leavitt's care center remains open for the handful of patients who must be seen in-person, he said. Those patients are screened beforehand and their temperatures taken before treatment.

Dr. Bulsiewicz's practice made the transition to telehealth after never having used the modality before COVID-19.

"This was a scramble," said Dr. Bulsiewicz, who posts about COVID-19 on social media. "We started from zero knowledge to implementation in less than a week."

Overall, the switch went smoothly, but Dr. Bulsiewicz said reimbursement challenges come with telehealth.

"The billing is not the same," he said. "You're doing the same work or more, and you're taking a reduced fee because of the antiquated fee structure that is forcing you to apply the typical rules of an office encounter."

He hopes CMS will alter the reimbursement schedule to temporarily pay on par with traditional evaluation and management codes based on medical complexity as opposed to documentation of physical exam. CMS has already expanded Medicare telehealth coverage to cover a wider range of health care services in light of the COVID-19 crisis and also broadened the range of communication tools that can be used, according to a March announcement.

In the meantime, many practices have applied for financial assistance programs. The AGA recently pushed the government for additional assistance to help struggling practices.

Dr. Jain hopes these assistance programs roll out quickly.

"If these don't get out there quick enough and big enough, we are going to see a massive wave of loss of independent practices and/or consolidation," he said. "I fear a death to small, independent practices because they're not going to have the financial wherewithal to tolerate this for too long."

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etary therapies" to a diet exclusively based on food allergens, tests for which are potentially inaccurate, the guidelines state.

Esophageal dilation is recommended for patients with stricture based on a systematic review in which 87% of patients improved with this therapy. However, dilation "does not address the esophageal inflammation associated with eosinophilic esophagitis," and the "assumption that no clinical improvement would occur if dilation was not performed likely overestimates [its] treatment benefit, given the reported symptom-placebo response noted in controlled trials," according to the guidelines. Moreover, the evidence for dilation "was considered low quality due to the retrospective, single-arm design of all but one of the reports, and the lack of a standard definition for what constitutes clinical improvement."

Anti-IgE therapy is not recommended – it failed to improve symptoms or esophageal eosinophilia in the only trial conducted to date. Because of a lack of evidence, the guidelines state that patients should receive only montelukast, cromolyn sodium, immunomodulators, anti–tumor necrosis factor therapies, or therapies targeting interleukin-5, IL-13, or IL-4 in the context of a clinical trial.

Eosinophilic esophagitis is triggered by exposure to food antigens and often overlaps with other atopic conditions, such as asthma, eczema, and allergic rhinitis. It has no approved treatments in the United States, although in 2018 the European Medicines Agency approved a budesonide tablet formulation.

The guideline authors disclosed no conflicts of interest.

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Multigene panel testing for colorectal cancer

For everyone

BY N. JEWEL SAMADDER, MD, MSC

Traditionally, health care structure has been directed predominantly toward treatment rather than prevention. Advances in genomic medicine offer the opportunity to deliver a more personalized, predictive, and preventive strategy toward colorectal cancer. Approximately 150,000 men and women are diagnosed with colorectal cancer (CRC) every year in the United States. An estimated 10%-15% of these cancers are likely attributable to hereditary (germline) causes. Several genes are associated with an increased risk of developing CRC, and those of key interest include those for Lynch syndrome, MLH1, MSH2, MSH6, PMS2, EPCAM; adenomatous polyposis conditions, APC, MUTYH, POLE, POLD1, NTHL1; hamartomatous polyposis syndromes, PTEN, SMAD4, STK11; and other rare cancer predisposition states where colorectal cancer is part of the phenotype, CHEK2 and TP532. In this article we will discuss why multigene panel testing should be considered for all patients with CRC.


Dr. Samadder

Dr. Samadder, MD, MSc, is a gastroenterologist in the division of gastroenterology and hepatology, Mayo Clinic, Phoenix. He is a consultant for Janssen Research & Development and Cancer Prevention Pharmaceuticals.

Not for everyone

BY CAROL A. BURKE, MD, AGAF, AND BRANDIE HEALD LEACH, MS


Dr. Burke


Ms. Leach

In unselected patients with colorectal cancer (CRC) undergoing multigene cancer panel testing (MGPT) approximately 10% have a germline pathogenic variant identified. The detection increases to 16% in those aged less than 50 years at time of diagnosis. The most common pathogenic variants detected are in Lynch syndrome genes, but other highly and moderately penetrant CRC and non-CRC pathogenic variants are diagnosed, many unsuspected because of lack of clinical features.

While MGPT is widely available, costs less than traditional sequencing, and casts a broad net for germline causes of cancer, downsides warrant consideration. These include higher detection of pathogenic variants for which management is uncertain, such as in moderate- or low-risk genes; finding variants of uncertain significance which are not actionable but require patient follow-up; and uncertainty in providing penetrance and cancer risk estimates when incidental pathogenic variants are identified.

Currently, MGPT is not suggested in at-risk relatives in families with a known pathogenic variant – cascade or single-site testing is recommended. In families with classic hereditary cancer phenotypes syndrome-specific testing is indicated. Individuals with mismatch-deficient tumors should be tested for Lynch syndrome. MGPT is not suggested in patients who would not benefit from testing (e.g., elderly, positive for comorbid disease, or no at-risk relatives).

Dr. Burke is with the department of gastroenterology, hepatology, and nutrition, Sanford R. Weiss Center for Hereditary Colorectal Neoplasia, Digestive Disease and Surgical Institute, Cleveland Clinic. Dr. Burke has no conflicts of interest.

Ms. Leach is with the Center for Personalized Genetic Healthcare, Sanford R. Weiss Center for Hereditary Colorectal Neoplasia, Digestive Disease and Surgical Institute, Cleveland Clinic. Ms. Leach serves on the advisory board of Invitae.

Dear colleagues and friends,


Dr. Kahi

I write to introduce to you the new Perspectives section of *GI & Hepatology News*.

A more appropriate description is perhaps old-new, because Perspectives is the continuation and legacy of *AGA Perspectives*, the content of which has been consolidated into *GI & Hepatology News*. Perspectives will continue to feature the point/counterpoint expert debates about an important GI topic, which has historically been immensely popular with readers. In this edition, experts from Mayo Clinic and Cleveland Clinic discuss the pros and cons of universal multigene panel testing for colorectal cancer. These debates never end with the publication itself, and I hope they will continue to stimulate further thought and discussion. As always, I welcome your comments and suggestions for future topics.

–Charles I. Kahi, MD, MS, AGAF

Dr. Kahi is professor of medicine at Indiana University School of Medicine, Indianapolis. He is also an Associate Editor for GI & Hepatology News.

Read more!
Please find full-length versions of these debates online at MDedge.com/gihepnews/perspectives.

COVID-19/IBD registry, fecal SARS-CoV-2 transmission, and more

BY LUCAS FRANKI
MDedge News

Registry traces COVID-19 in patients with IBD

A new international registry has been created so that gastroenterologists and other clinicians can report outcomes for patients with inflammatory bowel disease and COVID-19.

The SECURE-IBD registry includes those who are asymptomatic and detected only through public health screening; as of April 13, 2020, 483 cases (155 in the United States) of COVID-19 infections in IBD patients have been reported to the registry.

The registry was developed "to allow clinicians taking care of patients with [IBD] to report on the specifics of their cases, so that we could then quickly define what the impact is of this disease on our patients and determine how disease severity, medication, and specific demographics impact COVID-related outcomes in our population," said registry cofounder Erica Brenner, MD, a pediatric gastroenterology fellow at University of North Carolina at Chapel Hill.

FDA warns of fecal transplant transmission of SARS-CoV-2

The Food and Drug Administration has warned of the potential for SARS-CoV-2 transmission through fecal microbiota transplantation and that additional safety procedures may be required.

The risk of SARS-CoV-2 transmission remains unknown, but "several recent studies have documented the presence of SARS-CoV-2 ribonucleic acid (RNA) and/or SARS-CoV-2 virus in stool of infected individuals," the FDA said.

The FDA has issued several recommendations for any medically necessary usage of fecal microbiota transplantation involving stool samples donated after Dec. 1, 2019, including screening and testing donors for SARS-CoV-2, developing criteria

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to exclude donors who test positive, and providing informed consent to patients about the risk for SARS-CoV-2 transmission.

Hospitals keep doctors, nurses from speaking on COVID-19 experiences

Many hospital and hospital administrators are preventing health professionals from speaking out on personal protective equipment shortages and overwhelming COVID-19 cases, threatening them with discipline.

"The larger message is that patients are money," Nisha Mehta, MD, a physician advocate and community leader. "The corporate side of medicine rules out over the medicine side. Image and making sure there is a consistent cash flow trumps all else."

The AGA signed onto a message from the Council of Medical Specialty Societies, stating that all health care professionals should have access to protective equipment and be able to speak about the lack thereof without fear of retribution.

Nearly all COVID-19 admissions involve comorbidities

Almost 90% of hospital admissions for COVID-19 are in patients who have some other underlying condition, according to research from the Centers for Disease Control and Prevention.

Patients aged 65 years or older were most likely to have at least one comorbid condition at 94.4%, compared with 86.4% of those aged 50-64 years and 85.4% of patients who were aged 18-44 years. Hypertension was the most common comorbid condition overall, followed by cardiovascular disease and obesity; in the younger age groups, obesity was the most common comorbid condition.

Liver transplants should continue despite COVID-19

The American Association for the Study of Liver Diseases has recommended that liver transplants can continue during the COVID-19 pandemic, though consideration should be more limited.

The AASLD advised clinicians to "consider evaluating only patients with HCC [hepatocellular carcinoma] or those patients with severe disease and high MELD [model for end-stage liver disease] scores" in order to minimize exposure to the hospital environment.

Among other recommendations, the AASLD noted that symptoms of acute cellular rejection or disease flare cannot be presumed to be rejection or flares, as SARS-CoV-2 attacks the liver, and other urgent procedures such as biliary surgery should also continue as planned, while elective procedures should be postponed.

Mr. Franki, a Frontline associate editor, compiled this column from reports first published on MDedge.com and Medscape.com.

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