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Mayo Clinic Media Relations

These best practices advice statements were written because of increasing rates of bariatric/metabolic surgery, said Dr. Vivek Kumbhari.

AGA Clinical Practice Update

Early complications after bariatric/metabolic surgery

BY WILL PASS
MDedge News

The American Gastroenterological Association recently published a clinical practice update concerning endoscopic evaluation and management of early complications after bariatric/metabolic surgery.

The seven best practice advice statements, based on available evidence and expert opinion, range from a general call for high familiarity with available interventions to specific approaches for managing postoperative leaks.

According to lead author Vivek Kumbhari, MD, PhD, director of advanced endoscopy, department of gastroenterology and hepatology, Mayo Clinic, Jacksonville, Fla., and colleagues, the update was written in consideration of increasing rates of bariatric/metabolic surgery.

"Bariatric/metabolic sur-

See **Complications** · *page 20*

Novel oral inhibitor may block intestinal damage in celiac disease

BY HEIDI SPLETE
MDedge News

A novel oral inhibitor of transglutaminase 2 appears to block gluten-induced mucosal damage in patients with celiac disease at three different doses, based on proof-of-concept trial data from 132 patients.

"Currently, no drug therapy reliably prevents the effects of dietary gluten or has been approved by regulators to treat celiac disease," which remains an unmet need in these patients, many of whom struggle with symptoms even when they adhere to a gluten-free diet, wrote Detlef Schuppan, MD, of Johannes Gutenberg University of Mainz (Germany) and colleagues.

Celiac disease is driven in part by the enzyme transglutaminase 2, and a transglutaminase 2 inhibitor known as ZED1227 has been tested safely in phase 1 trials, they reported.

"ZED1227 targets the intestinal mucosa predominantly and thereby mediates protection; thus, it is unaffected by the complexity of the food matrix and is less dependent on the timing of ingestion of gluten-containing food," the researchers explained.

In a study published in the New England Journal of Medicine (2021 Jun 30. doi: 10.1056/NEJMoa2032441), the

See **Celiac** · *page 10*

ID of underlying link between red meat, CRC holds early intervention potential

BY WILL PASS
MDedge News

A mechanistic link between red meat consumption and colorectal cancer (CRC) has been identified in the form of an alkylating mutational signature, according to investigators.

This is the first time a colorectal mutational signature has been associated with a component of diet, which demonstrates the value of large-scale molecular epidemiologic studies and suggests potential for early, precision dietary intervention, reported lead author Carino Gurjao, MSc, of the Dana-Farber Cancer

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LETTER FROM THE EDITOR:

Catching up with ourselves

August is a month that we traditionally reserved for rest and recovery. But unfortunately, there seems to be little of either as we recover from COVID-19, deal with the care that has been delayed, try to understand issues of health inequity, and manage our hybrid reimbursement landscape. So let's set those issues aside for a bit and get back to science.


Dr. Allen

In this month's cover stories, we can read about some astounding accomplishments. A fantastic study comes from Dana-Farber Cancer Institute, Boston, where researchers found 900 colorectal cancers from nurses who had participated in the long-running Nurse's Health Studies. The researchers completed a whole-exome sequence on both normal and tumor tissue and then linked findings to the nutritional information contained in the Health Studies. With this information, they connected a tumor-associated mutation to the ingestion of red meat, which may suggest a causal link for the known association between red meat and CRC.

AGA has published a detailed clinical practice update about endoscopic management of complications after bariatric/metabolic surgery. Bariatric therapy is an area in which gastroenterologists should play an increasingly prominent role, in conjunction with our surgical and metabolic colleagues.

Finally, read about a novel oral therapy that may provide substantial relief for celiac patients. This randomized trial of a transglutaminase inhibitor was published in the New England Journal of Medicine and may provide new hope for this difficult condition.

Bariatric therapy is an area in which gastroenterologists should play an increasingly prominent role, in conjunction with our surgical and metabolic colleagues.

My term as Editor in Chief will end with the September issue. Megan Adams, MD, JD, MSc, will take over and provide insights and opinions beyond my past missives. I thank Christopher Palmer and the excellent Frontline Medical Communications staff who find topics and compose articles for us. Finally, the publication department at the American Gastroenterological Association is unparalleled, led by Erin Landis with Brook Simpson and now Jillian Schweitzer. I am fortunate to return to the AGA Governing Board as Secretary/Treasurer and work with our new president, John Inadomi, as well as Tom Serena, a great friend and AGA CEO.

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

aga community

Top patient case

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's a preview of a recent popular clinical discussion:

Brock Doubledee, DO, wrote the following in "Xeljanz for Crohn's":

"I have a 20-year-old female with moderately active Crohn's disease who has now failed Humira, Remicade, Entyvio and Stelara. The only option I know of for her at this time is Xeljanz, however her insurance will not approve this medication given its lack of FDA approval. I would be interested to know if anyone has any other recommended options or has had success with getting insurance approval. If you have had success I would appreciate any articles or guidance you have utilized to gain this approval."

See how AGA members responded and join the discussion: https://community.gastro.org/posts/24445.

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Can laparoscopic lavage beat resection for acute perforated diverticulitis?

BY HEIDI SPLETE
MDedge News

Severe complications at 5 years were no different for patients with perforated purulent diverticulitis who underwent laparoscopic peritoneal lavage or colon resection, according to data from 199 individuals treated at 21 hospitals in Norway and Sweden. But it may yet prove appropriate in the right patient.

Acute perforated diverticulitis with peritonitis remains a challenging complication with high morbidity and mortality among patients with diverticular disease, and bowel resection remains the standard of treatment, Najia Azhar, MD, of Skåne University Hospital, Malmö, Sweden, and colleagues wrote.

Short-term data suggest that laparoscopic lavage with drainage and antibiotics might be a viable alternative, but long-term data are lacking, they said.

In the Scandinavian Diverticulitis (SCANDIV) trial, published in JAMA Surgery (2021;156[2]:121-7), researchers randomized 101 patients to laparoscopic peritoneal lavage and 98 to colon resection. With 3 patients lost to follow-up, the final analysis included 73 patients who underwent laparoscopic lavage and 69 who underwent resection. The mean age of the lavage patients was 66.4 years, and 39 were men. The mean age of the resection patients was 63.5 years, and 36 were men. The primary outcome was severe complications – excluding stoma reversals and elective sigmoid resections because of recurrence – at an average of 5 years' follow-up. Secondary outcomes included stoma prevalence, diverticulitis recurrence, and secondary sigmoid resection.

Severe complications were similar for the lavage and resection groups (36% and 35%, respectively), as were the overall mortality rates (32% and 25%, respectively).

"Laparoscopic lavage is faster and cost-effective but leads to a higher reoperation rate and recurrence rate, often requiring secondary sigmoid resection."

The prevalence of stoma was significantly lower in the lavage group, compared with the resection group (8% vs. 33%, $P = .002$). However, secondary operations (including reversal of stoma) were similar between the lavage and resection groups, performed in 26 lavage patients (36%) versus 24 resection patients (35%).

Diverticulitis recurrence was significantly more common in the lavage, compared with the resection group (21% vs. 4%, $P = .004$), the researchers noted.

In the laparoscopic lavage group, 30% (n = 21) underwent a sigmoid resection; all but one of these occurred within a year of the index procedure, the researchers wrote. In addition, overall length of hospital stay was similar for both groups.

No significant differences in quality of life were noted between the groups, based on the EuroQoL-5D questionnaire or Cleveland Global Quality of Life scores.

Balance secondary pros and cons

Laparoscopic lavage is not common practice today in the United States, the researchers noted. In clinical practice guidelines issued in 2020, the American Society of Colon and Rectal Surgeons strongly recommend colectomy over laparoscopic lavage for the treatment of left-sided colonic diverticulitis (Dis Colon Rectum. 2020 Jun;63[6]:728-47). However, the European Society of Coloproctology's guidelines state that laparoscopic lavage is feasible for patients with peritonitis at Hinchey stage III (Colorectal Dis. 2020 Jul. doi: 10.1111/codi.15140).

The findings of the current study were limited primarily by the exclusion of 50% of eligible patients because of challenges associated with conducting randomized trials in emergency settings, the researchers noted. However, the number of excluded patients and their baseline characteristics after exclusion were very similar in the two groups, and the study represents the largest randomized trial to date to examine long-term outcomes in patients with perforated diverticulitis.

"Laparoscopic lavage is faster and cost-effective but leads to a higher reoperation rate and recurrence rate, often requiring secondary sigmoid resection," the researchers emphasized. Consequently, patients undergoing lavage should have consented for resection surgery.

The similar rates of severe complications and quality of life scores support laparoscopic lavage as an option for perforated purulent diverticulitis, but shared decision-making will be essential for better optimal patient management, the researchers concluded.

Similar outcomes, but unanswered questions

Even though the primary outcome of disease-related morbidity was similar for both groups, "the issue still remains regarding when and how, if ever, this therapeutic approach should be considered for purulent peritonitis," Kellie E. Cunningham, MD, and Brian S. Zuckerbraun, MD, both of the University of Pittsburgh, wrote in an accompanying editorial (JAMA Surg. 2021;156[2]:128).

Although laparoscopic lavage has the obvious advantages of avoiding a laparotomy and stoma, previous studies have shown a higher rate of early reoperations and recurrent diverticulitis, despite lower stoma prevalence and equal mortality rates, they said. In addition, "patients who are immunosuppressed or would be expected to have a higher mortality rate with failure to achieve definitive source control should likely not be offered this therapy."

A "philosophical" argument could be made in favor of laparoscopic lavage based on the potential consequences of early treatment failure, they wrote.

"Although one may consider the need for early reoperation a complication, some would argue it affects the minority of patients, thus avoiding the more morbid proce-

Continued on page 9

DDSEP 9
Digestive Diseases Self-Education Program

Quick Quiz

Q1. A 42-year-old male on chronic opiates for history of old spinal injury was seen for dysphagia. The patient reports having dysphagia for solids and liquids for the last 1 year without anorexia or weight loss. Patient denies symptoms of heartburn or regurgitation. A recent upper endoscopy was unrevealing. A high-resolution esophageal manometry was ordered.

Which of the following manometric findings have been shown to be associated with chronic opiate use?
A. Type 1 achalasia.
B. Ineffective esophageal motility.
C. Esophagogastric junction outflow obstruction.
D. Absent contractibility.

Q2. A 63-year-old female presents with a recent change in bowel habits. She previously had one formed bowel movement a day, but now has diarrhea three to four times a day with incontinence. She had prior normal colonoscopy 3 years ago.

Which of the following tests is not indicated as part of this evaluation?
A. CT scan.
B. Colonoscopy to evaluate for inflammation.
C. Anorectal manometry.
D. Digital rectal exam.
E. Endoanal ultrasound.

The answers are on page 30.

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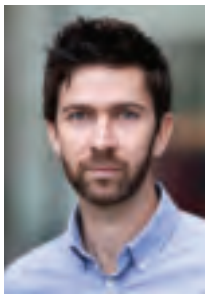
Inexpensive dye tracks digestive transit time

BY JIM KLING
MDedge News

When it comes to measuring gut transit time, blue dye could be a cost-effective and simple alternative to other, more burdensome methods.

The approach, which requires only fasting followed by eating dyed food, revealed an association between microbiome composition and transit time in healthy individuals, according to authors led by Francisco Asnicar, PhD, of the University of Trento (Italy) (Gut. 2021 Mar. doi: 10.1136/gutjnl-2020-323877). The researchers chose the blue food coloring over carmine red dye partly because of its vegetable origin and because the blue color makes it unlikely the recipient would mistake the coloring in stool as originating from some other food, such as beetroot.


Dr. Roager

Gut motility is connected to digestion, the immune system, the endocrine system, and gut microbiota, according to the authors. For example, some have suggested that transit time may affect postprandial glycemia and lipemia through a potential effect on nutrient absorption and gut microbiome composition (Nutrients. 2018 Feb 28;10[3]:275). "[This blue dye's] use therefore has the potential to provide another piece of the puzzle to advance precision medicine," the authors wrote.

Validated methods to measure transit time include scintigraphy, wireless motility capsule, radio-opaque markers, and breath testing, but they require specialized equipment and staff, participants must make at least one in-person visit, and they can be expensive.

Transit time's position in research

Those limitations may explain why the effect of transit time has been understudied, though it has gained momentum in recent years, according to Henrik Roager, PhD, who was asked to comment on the study. "I think it has become clear that it is probably one of the most important factors that explain the [microbiota] differences that we see from individual to individual," said Dr. Roager, of the department of nutrition, exercise, and sports at the University of Copenhagen.

The relationship is complex, since gut microbes may be releasing metabolites that can affect motility, which in turn would affect the microbes.

"I think it has become clear that [transit time] is probably one of the most important factors that explain the [microbiota] differences that we see from individual to individual."

Epidemiological studies made easier by dye or sweet corn could also reveal how diet interacts with the microbiome by including transit time as a variable. Transit time can vary from day to day, and Dr. Roager believes those variations may be linked to changes in the gut microbiome. With simpler techniques for measuring transit time, "I think we might be able to better identify effects of diets or drugs or lifestyle on the microbiome."

How the blue dye fared

The researchers analyzed data from 866 twins and unrelated adults from the United States and the United Kingdom who were enrolled in the PREDICT 1 study, which quantified metabolic responses to standardized meals. Participants underwent fasting and then ate two blue muffins, along with a glass of chocolate milk, then logged the first sign of blue coloring in their stool using an app. Participants also answered a questionnaire detailing the frequency and consistency of bowel movements. The researchers also conducted sequencing of stool samples to determine microbiome profile.

There was a strong correlation between stool consistency and frequency, as well as microbial diversity and the composition of the gut microbiome. The dye measurement identified different fast and slow transit time clusters (area under the receiver operating characteristic curve, 0.82), which were associated with the composition of the gut microbiome, including species like *Akkermansia muciniphila*, *Bacteroides* species, and *Alistipes* species (false discovery rate–adjusted *P* values < .01). Transit times measured with the blue dye was a better predictor of gut function than either stool consistency and stool frequency, suggesting that the dye may be a more useful method for large cohorts of healthy individuals.

Although associations with diet and cardiometabolic factors were more modest, longer transit times appear predictive of greater visceral fat and higher postprandial responses, "which are key measures of health."

The authors cited some limitations, including the fact that the blue-dye method has not yet been compared with other transit methodologies. However, the gut transit time in this study was found to be strongly correlated with stool consistency and frequency.

"To conclude, our findings indicate that the blue dye method is a novel, inexpensive and scalable method of gut transit assessment providing valuable gut health and metabolic insights," they wrote. "Its wide use in both research and clinical settings could facilitate the advancement of our understanding of gut function and its determinants, as well as the complex interactions between gut physiology and health outcomes."

The study authors received funding from a wide range of nonindustry sources. Dr. Roager had no relevant financial disclosures.

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Continued from page 3

dure with creation of a stoma at the index operation in the majority of patients," they noted. "Additionally, patients who underwent lavage that subsequently proceed to colectomy would have otherwise been offered this therapy initially at the time of the index operation."

More research is needed to answer questions such as which, if any, operative findings are associated with failure. In addition, an analysis of long-term cost benefits between the two options should be explored, the authors wrote.

Based on current evidence, shared decision-making is necessary, with individualized care and short- and long-term trade-offs taken into account, they wrote.

Gastroenterologist perspective: Study fills gap in follow-up data

In an interview, David A. Johnson, MD, professor of medicine at Eastern Virginia School of Medicine, Norfolk, said the study is important because data have been lacking on outcomes of laparoscopic lavage without resection. The findings represent "a major shift" in the growing consensus among surgeons that laparoscopic lavage is a viable option in appropriate patients, he said.

A key issue is the high rate of morbidity in patients who undergo traditional diverticulitis surgery. Complications can include wound infection and poor quality of life associated with stoma, Dr. Johnson said. Consequently, "a nonoperative approach from a patient perspective is certainly refreshing."

Dr. Johnson said he was surprised by how well the patients fared after lavage given the severity of the diverticulitis in the patient population. However, this may be in part because of the relatively small numbers of patients at highest risk for complications, such as those with diabetes or immunocompromising conditions.

Dr. Johnson also said he was struck by the fact that the adenocarcinomas in the lavage group were diagnosed within the first year after the procedure. "The cancer diagnosis shouldn't reflect on the lavage group," but emphasizes the importance of having an earlier colonoscopy, he noted.

Next steps for research might include identifying a standardized endpoint for lavage, and determining how expanded use of the procedure might impact community practice, Dr. Johnson said. In addition, more research is needed to more clearly define patients most likely to benefit from laparoscopic lavage.

The study was supported in part by the department of surgery at Skåne University Hospital, Akershus University Hospital, and a fellowship to one of the study coauthors from the Southeastern Norway Regional Health Authority. Lead author Dr. Azhar disclosed grants from the department of surgery of Skåne University Hospital. Dr. Cunninghamm, Dr. Zuckerbraum, and Dr. Johnson had no relevant financial disclosures.

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Drug could have 'profound impact'

Celiac *from page 1*

researchers assessed the safety and efficacy of three dose levels of ZED1227. Adults with controlled celiac disease were randomized to doses of 10 mg (41 patients), 50 mg (41 patients), and 100 mg (41 patients), and 40 patients received a placebo. Of these, 35, 39, 28, and 30 patients, respectively, had sufficient duodenal biopsy samples for analysis.

Patients underwent a daily gluten challenge of 3 g for 6 weeks. At the end of 6 weeks, the primary study endpoint of attenuation of gluten-induced mucosal damage was measured by the ratio of villus height to crypt depth.

Patients in all three treatment groups showed significant attenuation of mucosal damage. The change in the average ratio of villus height to crypt depth compared to placebo in the 10-mg, 50-mg, and 100-mg groups was 0.44, 0.49, and 0.48, respectively, with *P* values equal to .001 in the 10-mg group and less than .001 in the 50-mg and 100-mg groups.

Adverse events were similar across all treatment groups and the placebo group, with the exception of a rash in three patients in the 100-mg group. A total of 74 patients reported adverse events, and the most common were headache, nausea, diarrhea, vomiting, and abdominal pain. The investigators determined that from 34% to 55% of the adverse events across groups were related to the study drug or placebo.

Two patients developed serious adverse events that were deemed related to the study drug or placebo; one patient in the 50-mg group developed migraine with aura, and one placebo patient developed ventricular extrasystoles. The patients recovered after discontinuing the drug or placebo.

Secondary endpoints included intraepithelial lymphocyte density, the Celiac Symptom Index score, and the Celiac Disease Questionnaire score. Estimated changes in intraepithelial lymphocyte density, compared with placebo, were –2.7 cells per 100 epithelial cells in the 10-mg group, –4.2 cells per 100 epithelial cells in the 50-mg group, and –9.6 cells per 100 epithelial cells in the 100-mg group. Compared with those of patients taking placebo, the 6-week changes in Celiac Symptom Index scores and Celiac Disease Questionnaire scores suggested slight improvements in symptoms and quality of life for the 100-mg dose.

Findings were limited by several factors including missing data and loss of several patients to follow-up, as well as the short trial duration and use of controlled gluten ingestion, the researchers noted. Larger studies involving real-world conditions of minor gluten ingestion are needed to support the preliminary signs of safety and efficacy, they said.

> **"An absence of mucosal damage is a critical criterion to ensure the long-term health of a patient, and this clinical trial in celiac disease meets this important endpoint."**

Study strengths include high levels of patient adherence to the treatment and the gluten challenge, they said. "Future studies of ZED1227 in more patients are needed to provide additional evidence of the safety and efficacy of the drug, potentially in real-life conditions with minor gluten ingestion," they concluded.

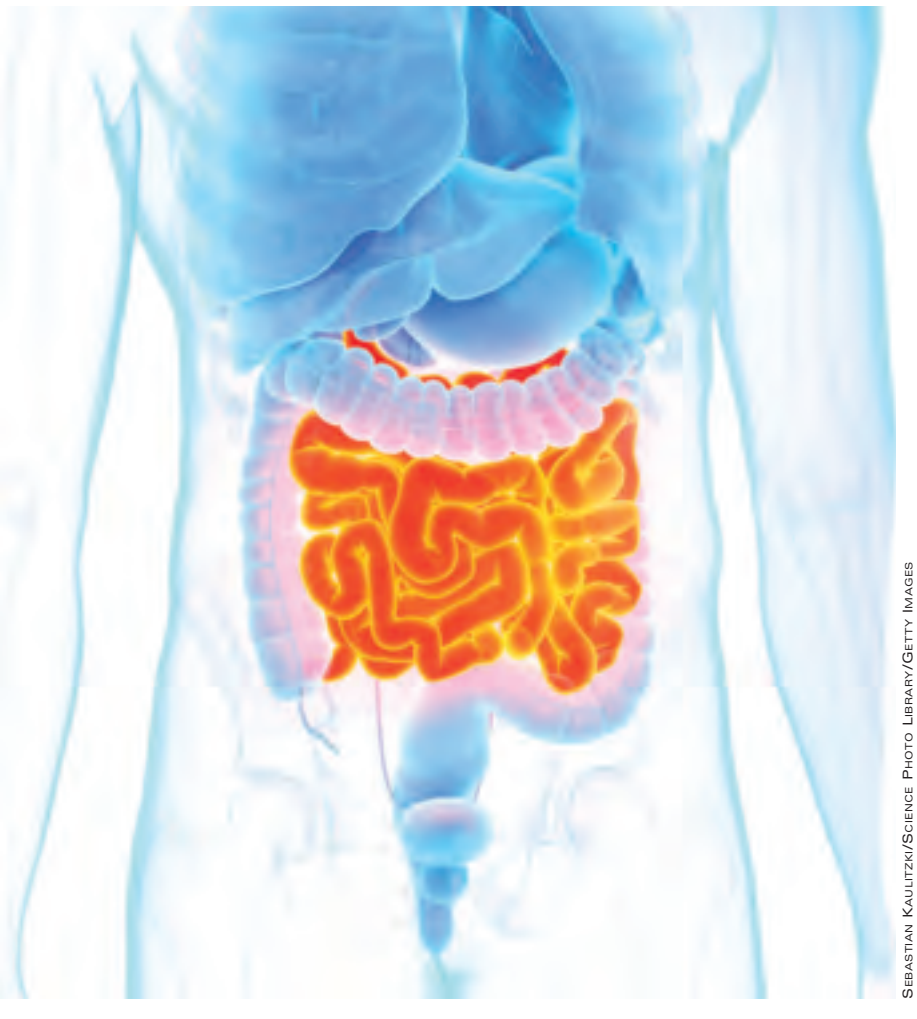
Translating potential into practice

"An absence of mucosal damage is a critical criterion to ensure the long-term health of a patient, and this clinical trial in celiac disease meets this important endpoint," Bana Jabri, MD, of the University of Chicago, wrote in an accompanying editorial (N Engl J Med. 2021 Jun 30. doi: 10.1056/NEJMe2107502).

The primary endpoint of no mucosal damage is "especially notable because it was achieved under a controlled gluten challenge, albeit with a relatively moderate amount of gluten (a regular diet contains 12 g of gluten daily, whereas the challenge involved 3 g daily) and for a short period of time," Dr. Jabri said. The reduction of disease-associated symptoms and apparent improvement in quality of life with 100-mg dose added value to the findings, she said.

Future research areas include whether cross-reactive T cells, which were not analyzed in the current study, might "expand and become pathogenic after a long-term gluten challenge," Dr. Jabri noted.

However, "ZED1227 is the first nondietary treatment that has preliminarily shown the capacity to prevent mucosal damage in persons with celiac disease," she said.



Sebastian Kaulitzki/Science Photo Library/Getty Images

"Although this trial is very encouraging, whether treatment with ZED1227, and more generally transglutaminase 2 inhibition, in patients with celiac disease will be efficient in real life and during long-term gluten exposure remains to be determined," Dr. Jabri concluded.

Need for data on dosing consistency

"Celiac disease affects up to 2% of the population in many countries, and the main therapy of celiac disease is avoidance of gluten," Kim L. Isaacs, MD, PhD, AGAF, of the University of North Carolina, Chapel Hill, said in an interview. "This is challenging due to the ubiquitous nature of gluten in many food products," she said. "Restrictive eating also affects social interaction which is often focused around food," she added. "Availability of an oral therapy that is effective to treat celiac in the face of gluten exposure will have a profound impact on patients in terms of liberalization of dietary intake."

Overall, "the changes in the villus height to crypt depth was similar between all the active treatment groups, whereas there was a dose-dependent reduction in transepithelial lymphocyte density," Dr. Isaacs noted. "The symptom improvement was greatest in the 100-mg group, suggesting that symptoms may be related to a greater extent to the lymphocyte density than the minimal differences in villus height to crypt depth ratios seen in the active treatment groups."

Potential barriers to the use of the treatment include cost because "this will need to be a daily long-term therapy," said Dr. Isaacs. "Compliance is a potential barrier as well," she said. "This study looks at daily administration of the transglutaminase 2 inhibitor and shows a benefit, but it is not clear whether missing doses of the medication will have a prolonged impact on efficacy," she emphasized. Consequently, long-term efficacy studies are needed, Dr. Isaacs said. Other research questions to answer include whether patients will become refractory to the beneficial effects over time, the effect of missing doses, and whether patients would lose all the benefits of the therapy if dosing is not consistent, she emphasized.

The study was funded by Dr. Falk Pharma. The researchers, as well as Dr. Jabri and Dr. Isaacs, had no financial conflicts to disclose. Dr. Isaacs is on the editorial advisory board of GI & Hepatology News.

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Microscopic colitis: A common, yet often overlooked, cause of chronic diarrhea

BY JUNE TOME, MD; AMRIT K. KAMBOJ, MD; AND DARRELL S. PARDI, MD, MS, AGAF

Microscopic colitis is an inflammatory disease of the colon and a frequent cause of chronic or recurrent watery diarrhea, particularly in older persons. MC consists of two subtypes, collagenous colitis (CC) and lymphocytic colitis (LC). While the primary symptom is diarrhea, other signs and symptoms such as abdominal pain, weight loss, and dehydration or electrolyte abnormalities may also be present depending on disease severity.[1] In MC, the colonic mucosa usually appears normal on colonoscopy, and the diagnosis is made by histologic findings of intraepithelial lymphocytosis with (CC) or without (LC) a prominent subepithelial collagen band. The management approaches to CC and LC are similar and should be directed based on the severity of symptoms.[2] We review the epidemiology, risk factors, pathophysiology, diagnosis, and clinical management for this condition, as well as novel therapeutic approaches.

Epidemiology

Although the incidence of MC increased in the late 20th century, more recently, it has stabilized with an estimated incidence varying from 1 to 25 per 100,000 person-years.[3-5] A recent meta-analysis revealed a pooled incidence of 4.85 per 100,000 persons for LC and 4.14 per 100,000 persons for CC.[6] Proposed explanations for the rising incidence in the late 20th century include improved clinical awareness of the disease, possible increased use of drugs associated with MC, and increased performance of diagnostic colonoscopies for chronic diarrhea. Since MC is now well recognized, the recent plateau in incidence rates may reflect decreased detection bias.

The prevalence of MC ranges from 10% to 20% in patients undergoing colonoscopy for chronic watery diarrhea.[6,7] The prevalence of LC is approximately 63.1 cases per 100,000 person-years and, for CC, is 49.2 cases per 100,000 person-years.[6-8] Recent studies have demonstrated increasing prevalence of MC likely resulting from an aging population.[9,10]

Risk stratification

Female gender, increasing age, concomitant autoimmune disease, and the use of certain drugs, including NSAIDs, proton pump inhibitors (PPIs), statins, and selective serotonin reuptake inhibitors (SSRIs), have been associated with an increased risk of MC.[11,12] Autoimmune disorders, including celiac disease (CD), rheumatoid arthritis, hypothyroidism, and hyperthyroidism, are more common in patients with MC. The association with CD, in particular, is clinically important, as CD is associated with a 50-70 times greater risk of MC, and 2%-9% of patients with MC have CD.[13,14]

Several medications have been associated with MC. In a British multicenter prospective study, MC was associated with the use of NSAIDs, PPIs, and SSRIs[15]; however, recent studies have questioned the association of MC with some of these medications, which might worsen diarrhea but not actually cause MC.[16]

An additional risk factor for MC is smoking. A recent meta-analysis demonstrated that current and former smokers had an increased risk of MC (odds ratio, 2.99; 95% confidence interval, 2.15-4.15 and OR, 1.63; 95% CI, 1.37-1.94, respectively), compared with nonsmokers.[17] Smokers develop MC at a younger age, and smoking is associated with increased disease severity and decreased likelihood of attaining remission.[18,19]

Dr. Tome is with the department of internal medicine at the Mayo Clinic, Rochester, Minn. **Dr. Kamboj** and **Dr. Pardi** are with the division of gastroenterology and hepatology at the Mayo Clinic. Dr. Pardi has grant funding from Pfizer, Vedanta, Seres, Finch, Applied Molecular Transport, and Takeda and has consulted for Vedanta and Otsuka. The other authors have no conflicts of interest to report.

Pathogenesis

The pathogenesis of MC remains largely unknown, although there are several hypotheses. The leading proposed mechanisms include reaction to luminal antigens, dysregulated collagen metabolism, genetic predisposition, autoimmunity, and bile acid malabsorption.

MC may be caused by abnormal epithelial barrier function, leading to increased permeability and reaction to luminal antigens, including dietary antigens, certain drugs, and bacterial products,[20,21] which themselves lead to the immune dysregulation and intestinal inflammation seen in MC. This mechanism may explain the association of several drugs with MC. Histological changes resembling LC are reported in patients with CD who consume gluten; however, large population-based studies have not found specific dietary associations with the development of MC.[22]

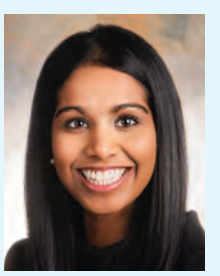
Another potential mechanism of MC is dysregulated collagen deposition. Collagen accumulation in the subepithelial layer in CC may result from increased levels of fibroblast growth factor, transforming growth factor–beta and vascular endothelial growth factor.[23] Nonetheless, studies have not found an association between the severity of diarrhea in patients with CC and the thickness of the subepithelial collagen band.

Thirdly, autoimmunity and genetic predisposition have been postulated in the pathogenesis of MC. As previously discussed, MC is associated with several autoimmune diseases and predominantly occurs in women, a distinctive feature of autoimmune disorders. Several studies have demonstrated an association between MC and HLA-DQ2

Continued on following page

Microscopic colitis is a cause of chronic or recurrent watery diarrhea that occurs more commonly in women, older individuals, or those with concomitant autoimmune diseases. Specific medications such as NSAIDs, proton pump inhibitors, and selective serotonin uptake inhibitors may trigger symptoms. Diagnosis can be elusive as colonic mucosa typically appears endoscopically normal, and the pathognomonic findings are histologic.

The In Focus article for August, which is brought to you by The New Gastroenterologist, provides a detailed review on microscopic colitis written by Dr. June Tome, Dr. Amrit K. Kamboj, and Dr. Darrell S. Pardi (Mayo Clinic, Rochester, Minn.). This article describes the risk factors, pathogenesis, and diagnosis of the disease. Importantly, the authors also elucidate a comprehensive management approach, which can be challenging given the frequently relapsing and remitting nature of its clinical course.



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

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and -DQ3 haplotypes,[24] as well as potential polymorphisms in the serotonin transporter gene promoter.[25] It is important to note, however, that only a few familial cases of MC have been reported to date.[26]

Lastly, bile acid malabsorption may play a role in the etiology of MC. Histologic findings of inflammation, along with villous atrophy and collagen deposition, have been reported in the ileum of patients with MC[27,28]; however, because patients with MC without bile acid malabsorption may also respond to bile acid binders such as cholestyramine, these findings, unlikely to be the sole mechanism explaining the development of the disease.

Despite the different proposed mechanisms for the pathogenesis of MC, no definite conclusions can be drawn because of the limited size of these studies and their often conflicting results.

Clinical features

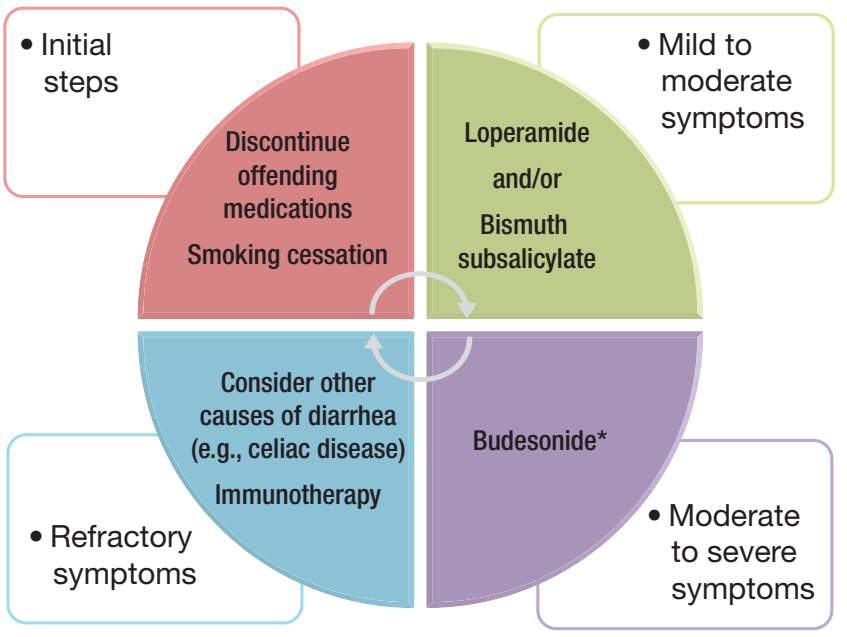
Clinicians should suspect MC in patients with chronic or recurrent watery diarrhea, particularly in older persons. Other risk factors include female gender, use of certain culprit medications, smoking, and presence of other autoimmune diseases. The clinical manifestations of MC subtypes LC and CC are similar with no significant clinical differences.[1,2] In addition to diarrhea, patients with MC may have abdominal pain, fatigue, and dehydration or electrolyte abnormalities depending on disease severity. Patients may also present with fecal urgency, incontinence, and nocturnal stools. Quality of life is often reduced in these patients, predominantly in those with severe or refractory symptoms.[29,30] The natural course of MC is highly variable, with some patients achieving spontaneous resolution after one episode and others developing chronic symptoms.

Diagnosis

The differential diagnosis of chronic watery diarrhea is broad and includes malabsorption/maldigestion, inflammatory bowel disease (IBD), irritable bowel syndrome, and medication side effects. In addition, although gastrointestinal infections typically cause acute or subacute diarrhea, some can present with chronic diarrhea. Malabsorption/maldigestion may occur because of CD, lactose intolerance, and pancreatic insufficiency, among other conditions. A thorough history, regarding recent antibiotic and medication use, travel, and immunosuppression, should be obtained in patients with chronic diarrhea. Additionally, laboratory and endoscopic evaluation with random biopsies of the colon can further help differentiate these diseases from MC. A few studies suggest fecal calprotectin may be used to differentiate MC from other noninflammatory conditions such as irritable bowel syndrome, as well as to monitor disease activity. This test is not expected to distinguish MC from other inflammatory causes of diarrhea, such as IBD, and therefore, its role in clinical practice is uncertain.[31]

The diagnosis of MC is made by biopsy of the colonic mucosa demonstrating characteristic pathologic features.[32] Unlike in diseases such as Crohn's disease or ulcerative colitis, the colon usually appears normal in MC, although mild nonspecific changes, such as erythema or edema, may be visualized. There is no consensus on the ideal location to obtain biopsies for MC or whether biopsies from both the left and the right colon are required.[2,33] The procedure of choice for the diagnosis of MC is colonoscopy with random biopsies taken throughout the colon. More limited evaluation by flexible sigmoidoscopy with biopsies may miss cases of MC as inflammation and collagen thickening are not necessarily uniform throughout the colon; however, in a patient that has undergone a recent colonoscopy for colon cancer screening without colon biopsies, a flexible sigmoidoscopy may be a reasonable next test for evaluation of MC, provided biopsies are obtained above the rectosigmoid colon.[34]

The MC subtypes are differentiated based on histology. The hallmark of LC is less than 20 intraepithelial lymphocytes per 100 surface epithelial cells (normal, less than 5) (Figure 1A). CC is characterized by a thickened subepithelial collagen band greater than 7-10 micrometers (normal, less than 5) (Figure 1B). For a subgroup of patients with milder abnormalities that do not meet these histological criteria, the terms "microscopic colitis, not otherwise specified" or "microscopic colitis, incomplete" may be used.[35] These patients often respond to standard treatments for MC. There is an additional subset of patients with biopsy demonstrating features of both CC and LC simultaneously, as well as patients transitioning from one MC subtype to another over time.[32,35]



*Budesonide should be considered for induction and maintenance therapy, if necessary, to control patient symptoms.

Figure 2: Management approach to microscopic colitis is charted.

Courtesy Dr. June Tome, Dr. Amrit K. Kamboj, and Dr. Darrell S. Pardi

Management approach

The first step in management of patients with MC includes stopping culprit medications if there is a temporal relationship between the initiation of the medication and the onset of diarrhea, as well as encouraging smoking cessation. These steps alone, however, are unlikely to achieve clinical remission in most patients. A stepwise pharmacological approach is used in the management of MC based on disease severity (Figure 2). For patients with mild symptoms, antidiarrheal medications, such as loperamide, may be helpful.[36] Long-term use of loperamide at therapeutic doses no greater than 16 mg daily appears to be safe if required to maintain symptom response. For those with persistent symptoms despite antidiarrheal medications, bismuth subsalicylate at three 262-mg tablets three times daily for 6-8 weeks can be considered. Long-term use of bismuth subsalicylate is not advised, especially at this dose, because of possible neurotoxicity.[37]

For patients refractory to the above treatments or those with moderate to severe symptoms, an 8-week course of budesonide at 9 mg daily is the first-line treatment.[38] The dose was tapered before discontinuation in some studies but not in others. Both

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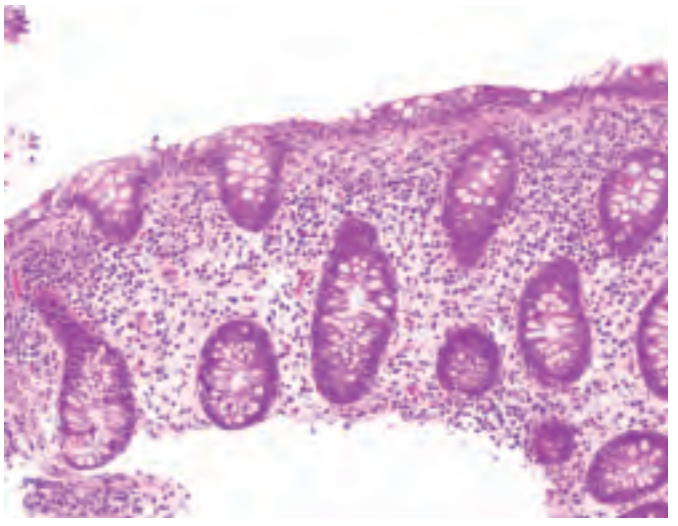

Figure 1A: Histopathology is shown for lymphocytic colitis.

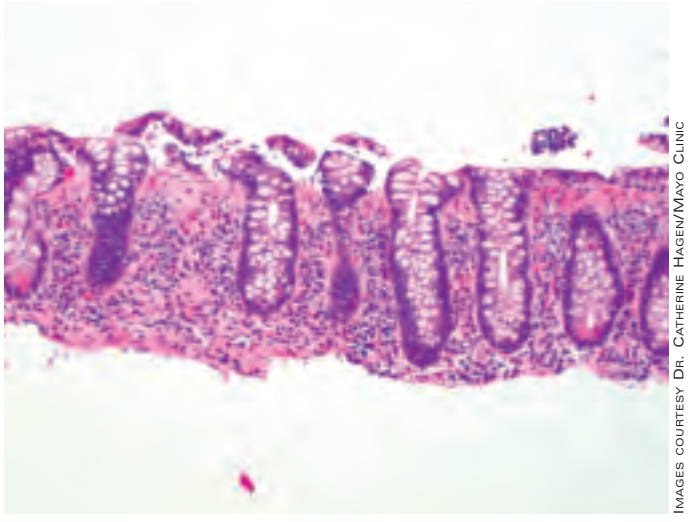

Figure 1B: Histopathology is shown for collagenous colitis.

Images courtesy Dr. Catherine Hagen/Mayo Clinic

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strategies appear effective. A recent meta-analysis of nine randomized trials demonstrated pooled ORs of 7.34 (95% CI, 4.08-13.19) and 8.35 (95% CI, 4.14-16.85) for response to budesonide induction and maintenance, respectively.[39]

Cholestyramine is another medication considered in the management of MC and warrants further investigation. To date, no randomized clinical trials have been conducted to evaluate bile acid sequestrants in MC, but they should be considered before placing patients on immunosuppressive medications. Some providers use mesalamine in this setting, although mesalamine is inferior to budesonide in the induction of clinical remission in MC.[40]

Despite high rates of response to budesonide, relapse after discontinuation is frequent (60%-80%), and time to relapse is variable.[41,42] The American Gastroenterological Association recommends budesonide for maintenance of remission in patients with recurrence following discontinuation of induction therapy. The lowest effective dose that maintains resolution of symptoms should be prescribed, ideally at 6 mg daily or lower.[38] Although budesonide has a greater first-pass metabolism, compared with other glucocorticoids, patients should be monitored for possible side effects including hypertension, diabetes, and osteoporosis, as well as ophthalmologic disease, including cataracts and glaucoma.

For those who are intolerant to budesonide or have refractory symptoms, concomitant disorders such as CD that may be contributing to symptoms must be excluded. Immunosuppressive medications – such as thiopurines and biologic agents, including tumor necrosis factor–alpha inhibitors or vedolizumab – may be considered in refractory cases.[43,44] Of note, there are limited studies evaluating the use of these medications for MC. Lastly, surgeries including ileostomy with or without colectomy have been performed in the most severe cases for resistant disease that has failed numerous pharmacological therapies.[45]

Patients should be counseled that, while symptoms from MC can be quite bothersome and disabling, there appears to be a normal life expectancy and no association between MC and colon cancer, unlike with other inflammatory conditions of the colon such as IBD.[46,47]

Conclusion and future outlook

As a common cause of chronic watery diarrhea, MC will be commonly encountered in primary care and gastroenterology practices. The diagnosis should be suspected in patients presenting with chronic or recurrent watery diarrhea, especially with female gender, autoimmune disease, and increasing age. The management of MC requires an algorithmic approach directed by symptom severity, with a subgroup of patients requiring maintenance therapy for relapsing symptoms. The care of patients with MC will continue to evolve in the future. Further work is needed to explore long-term safety outcomes with budesonide and the role of immunomodulators and newer biologic agents for patients with complex, refractory disease.

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

New Clinical Practice Update Expert Review: Management of bleeding gastric varices

AGA has released a new Clinical Practice Update Expert Review providing 12 best practice advice statements on the diagnosis and management of bleeding gastric varices. The evidence-based advice includes the following:

- Initial therapy for bleeding gastric varices should focus on acute hemostasis for hemodynamic stabilization with a plan for further diagnostic evaluation and/or transfer to a tertiary care center with expertise in gastric varices management.
- Following initial endoscopic hemostasis, cross-sectional (magnetic resonance or CT) imaging with portal venous contrast phase should be obtained to determine vascular anatomy, including the presence or absence of portosystemic shunts and gastrorenal shunts.
- Determination of definitive therapy for bleeding gastric varices should be based on endoscopic appearance of the gastric varix, the underlying vascular anatomy, presence of comorbid portal hypertensive complications, and available local resources. This is ideally done via a multidisciplinary discussion between the GI or hepatologist and the interventional radiologist.

In this AGA Clinical Practice Update Expert Review, the experts also suggest adding an estimate of variceal size and high-risk stigmata (discolored marks, platelet plugs) to the Sarin classification when describing patients' gastric varices.

Read the full list of the best practice advice statements in the AGA Clinical Practice Update on Management of Bleeding Gastric Varices: Expert Review (Clin Gastroenterol Hepatol. 2021 Jun;19[6]:1098-107.e1).

FatCamera/Getty Images

AGA journals select new editorial fellows

The AGA journals Gastroenterology, Clinical Gastroenterology and Hepatology (CGH), Cellular and Molecular Gastroenterology and Hepatology (CMGH), and Techniques and Innovations in Gastrointestinal Endoscopy (TIGE) recently selected the recipients of their editorial fellowships, which runs from July 2021 through June 2022. The AGA editorial fellowship program is in its fourth year.

- Amisha Ahuja, MD (Gastroenterology)
- Helenie Kefalalkes, MD (Gastroenterology)
- Katherine Falloon, MD (CGH)
- Judy Trieu, MD, MPH (CGH)
- Lindsey Kennedy, PhD (CMGH)
- Vivian Ortiz, MD (CMGH)
- Sagarika Satyavada, MD (TIGE)
- Eric Swei, MD (TIGE)

Tetra Images/Getty Images

Five reasons to update your will

You have a will, so you can rest easy, right? Not necessarily. If your will is outdated, it can actually cause more harm than good. Even though it can provide for some contingencies, an old will can't cover every change that may have occurred since it was first drawn. Here are five reasons to update your will.

Keep it current

When life changes, so should your will. Ensure that this important document matches your current wishes by reviewing it every few years.

Take a look at what has changed

Professionals advise that you review your will every few years and more often if situations such as the following five have occurred since you last updated your will.

- **Family changes.** If you've had any changes in your family situation, you will probably need to update your will. Events such as marriage, divorce, death, birth, adoption, or a falling out with a loved one may affect how your estate will be distributed, who should act as guardian for your dependents, and who should be named as executor of your estate.
- **Relocating to a new state.** The laws among the states vary. Moving to a new state or purchasing property in another state can affect your estate plan and how property in that state will be taxed and distributed.
- **Changes in your estate's value.** When you made your will, your assets may have been relatively modest. Now the value may be larger and your will no longer reflects how you would like your estate divided.
- **Tax law changes.** Federal and state legislatures are continually tinkering with federal estate and state inheritance tax laws. An old will may fail to take advantage of strategies that will minimize estate taxes.
- **You want to support a favorite cause.** If you have developed a connection to a cause, you may want to benefit a particular charity with a gift in your estate. Contact us for sample language you can share with your attorney to include a gift to us in your will.

Get the help you need

To make sure your will accomplishes all you intend, seek the help of an attorney who specializes in estate planning. Already finalized your charitable distribution to the AGA Research Foundation? Send us your letter of intent at foundation@gastro.org.

Best practices: Consider endoscopy first

Complications *from page 1*

gery is unmatched with respect to its weight loss and metabolic benefits," the investigators wrote in Clinical Gastroenterology and Hepatology (2021 Mar 16. doi: 10.1016/j.cgh.2021.03.020). "The selection criteria will continue to broaden, likely resulting in increasing numbers of less robust patients undergoing surgery (e.g., children, elderly, and those with significant cardiorespiratory comorbidities)."

Although the 90-day overall complication rate across all patients undergoing bariatric/metabolic surgery is only 4%, Dr. Kumbhari and colleagues noted that this rate is considerably higher, at 20.1%, among patients aged older than 65 years.

"As utilization escalates, so will the number of patients who suffer early complications," they wrote.

The first three items of best practice advice describe who should be managing complications after bariatric/metabolic surgery, and how.

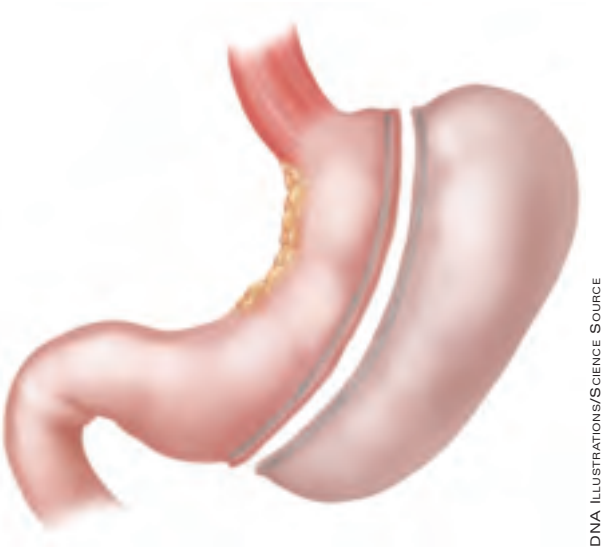
Foremost, Dr. Kumbhari and colleagues called for a multidisciplinary approach; they suggested that endoscopists should work closely with related specialists, such as bariatric/metabolic surgeons and interventional radiologists.

"Timely communication between the endoscopist, radiologist, surgeon, nutritionists, and inpatient medical team or primary care physician will result in efficient, effective care with prompt escalation and deescalation," they wrote. "Daily communication is advised."

The next two best practice advice statements encourage high familiarity with endoscopic treatments, postsurgical anatomy, interventional radiology, and surgical interventions, including risks and benefits of each approach.

"The endoscopist should ... have expertise in interventional endoscopy techniques, including but not limited to using concomitant fluoroscopy, stent deployment and retrieval, pneumatic balloon dilation, incisional therapies, endoscopic suturing, and managing percutaneous drains," the investigators wrote. "Having the ability to perform a wide array of therapies will enhance the likelihood that the optimal endoscopic strategy will be employed, as opposed to simply performing a technique with which the endoscopist has experience."

Following these best practices, Dr. Kumbhari and colleagues advised screening patients with postoperative complications for comorbidities, both medical in nature (such as infection) and psychological.



DNA Illustrations/Science Source

"Patients often have higher depression and anxiety scores, as well as a lower physical quality of life, and medical teams sometimes neglect the patient's psychological state," they wrote. "It is imperative that the multidisciplinary team recognize and acknowledge the patient's psychological comorbidities and engage expertise to manage them."

Next, the investigators advised that endoscopic intervention should be considered regardless of time interval since surgery, including the immediate postoperative period.

"Endoscopy is often indicated as the initial therapeutic modality, and it can safely be performed," Dr. Kumbhari and colleagues wrote in the update.

"When endoscopy is performed, it is advised to use carbon dioxide for insufflation. Caution should be used when advancing the endoscope into the small bowel, as it is best to minimize pressure along the fresh staple lines. In cases in which the patient is critically ill or the interventional endoscopist does not have extensive experience with such a scenario, the endoscopy should be performed in the operating room with a surgeon present (preferably the surgeon who performed the operation)."

Dr. Kumbhari and colleagues discussed functional stenosis, which can precipitate and propagate leaks. They noted that "downstream stenosis is frequently seen at the level of the incisura angularis or in the proximal stomach when a sleeve gastrectomy is performed in a patient with a prior laparoscopic adjustable gastric band."

To address such stenosis, the update calls for "aggressive dilation" using a large pneumatic balloon, preferably with fluoroscopy to make sure the distal end of the balloon does not cross the pylorus. The investigators noted that endoscopic suturing may be needed if a tear involving the muscularis propria is encountered.

Lastly, the clinical practice update offers comprehensive guidance for managing staple-line leaks, which "most commonly occur along the staple line of the proximal stomach."

As leaks are thought to stem from ischemia, "most leaks are not present upon completion of the operation, and they develop over the subsequent weeks, often in the setting of downstream stenosis," the investigators wrote.

To guide management of staple-line leaks, the investigators presented a treatment algorithm that incorporates defect size, time since surgery, and presence or absence of stenosis.

For example, a defect smaller than 10 mm occurring within 6 weeks of surgery and lacking stenosis may be managed with a percutaneous drain and diversion. In contrast, a defect of similar size, also without stenosis, but occurring later than 6 weeks after the initial procedure, should be managed with endoscopic internal drainage or vacuum therapy.

"Clinicians should recognize that the goal for endoscopic management of staple-line leaks is often not necessarily initial closure of the leak site, but rather techniques to promote drainage of material from the perigastric collection into the gastric lumen such that the leak site closes by secondary intention," wrote Dr. Kumbhari and colleagues.

The clinical practice update was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board. The investigators disclosed relationships with Boston Scientific, Medtronic, Apollo Endosurgery, and others.

ginews@gastro.org

Semaglutide boosts weight loss following endoscopic gastroplasty

BY PAM HARRISON

FROM DDW 2021

Combining minimally invasive endoscopic sleeve gastroplasty with a weekly injection of the glucagonlike peptide–1 agonist semaglutide (Ozempic, Novo Nordisk) leads to significantly greater weight loss than ESG alone in patients with diabetes and excess weight who are not candidates for bariatric surgery, new research shows.

"We found that by adding the GLP-1 agonist [semaglutide], we could increase weight loss from, on average, about 16%-18% of total body weight with ESG alone to up to 27%, so it's a great metabolic combination," said Anna Carolina Hoff, MD, founder and clinical director of Angioskope Brazil in São José dos Campos, who presented the findings at the annual Digestive Disease Week® (DDW).

ESG is a surrogate for laparoscopic sleeve gastrectomy that can offer the benefits of such a procedure to those who don't qualify for, or don't wish to pursue, bariatric surgery. It can be performed at an earlier stage of disease, in those with a body mass index of 30 mg/kg^2, whereas generally people are not offered bariatric procedures unless they have a BMI of at least 35 with comorbidities or a BMI of at least 40 if they do not have any.

The Brazilian study involved 58 patients with obesity or overweight who also had diabetes and were undergoing minimally invasive ESG; they were further randomized to receive semaglutide or placebo. Twelve months after ESG, patients who received additional semaglutide lost 86.3% of their excess body

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Modifiable risk meets biology

Link *from page 1*

Institute and Harvard Medical School, both in Boston, and colleagues.

"Red meat consumption has been consistently linked to the incidence of colorectal cancer," the investigators wrote in Cancer Discovery (2021 Jun 17. doi: 10.1158/2159-8290.CD-20-1656). "The suggested mechanism is mutagenesis through alkylating damage induced by N-nitroso-compounds (NOCs), which are metabolic products of blood heme iron or meat nitrites/nitrates. Nevertheless, this mutational damage is yet to be observed directly in patients' tumors."

To this end, the investigators turned to three long-term, large-scale, prospective cohort studies: the Nurses' Health Studies I and II, and the Health Professionals Follow-Up Study. These databases include nearly 300,000 individuals with follow-up dating back as far as 1976. The investigators identified 900 cases of primary, untreated CRC with adequate tissue for analysis, then, for each case, performed whole-exome sequencing on both tumor tissue and normal colorectal tissue.

This revealed an alkylating mutational signature previously undescribed in CRC that was significantly associated with consumption of red meat prior to diagnosis, but not other dietary or lifestyle factors. The signature occurred most frequently in tumors and normal crypts in the distal colon and rectum.

According to the investigators, the presence of the alkylating signature in normal colorectal crypts "suggests that mutational changes due to such damage may start to occur early in the path of colorectal carcinogenesis."

Further analysis showed that tumors harboring common KRAS and PIK3CA driver mutations had the highest levels of alkylating damage, with higher levels predicting worse survival.

"These results ... further implicate the role of red meat in CRC initiation and progression," the investigators concluded.

Early findings, important implications

Co–senior author Kana Wu, MD, PhD, principal research scientist in the department of nutrition at Harvard School of Public Health, Boston, noted that these are early findings, although they may pave the way toward new dietary recommendations and methods of food production.

"While more detailed analysis needs to be conducted, and our results need to be confirmed in other studies, this study is a promising first step to better understand the biological mechanisms underlying the role of red and processed meats in colorectal cancers," Dr. Wu said in an interview. "It is important to gain more insight into the biological mechanisms so we can improve dietary guidelines for cancer prevention and guide food reformulation efforts to lower cancer risk."

For now, Dr. Wu predicted that standing dietary recommendations will remain unchanged.

"This study will not alter current diet recommendations to limit intake of red and processed meats," Dr. Wu said, referring to similar recommendations across several organizations, including the American Heart Association, the World Cancer Research Fund/American Institute for Cancer Research, and the American Cancer Society.

"For example," Dr. Wu said, "the WCRF/AICR recommends limiting consumption of red and processed meat to 'no more than moderate amounts [12-18 ounces per week] of red meat, such as beef, pork, and lamb, and [to] eat little, if any, processed meat.' "

Possible biomarker?

According to Patricia Thompson-Carino, PhD, deputy director of the Stony Brook (N.Y.) Cancer Center, the study provides convincing evidence linking red meat consumption with development of CRC.

"Higher frequency of the signature in the distal colon is compelling for its consistency with epidemiologic evidence," Dr. Thompson-Carino said in an interview. "Combined with the observed worse survival in patients harboring the signature and association with oncogenic KRAS and PIK3CA driver mutations, this study significantly elevates the biological plausibility that red meat is a modifiable source of NOC mutagenicity and carcinogenesis in humans."

The signature could be used as a biomarker to detect exposure to NOCs, and susceptibility to CRC, she added.

Still, Dr. Thompson-Carino suggested that more work is needed to fully elucidate underlying mechanisms of action, which are needed to accurately shape dietary guidance.

AGA Resource

Help your patients understand colorectal cancer prevention and screening options by sharing AGA's patient education from the GI Patient Center: www.gastro.org/CRC.

"Key to advancing red meat dietary recommendations will be understanding the relationships between the new mutation signature and the NOCs derived from red meat and their source, whether endogenous [for example, intestinal N-nitrosation] or exogenous [for example, chemical preservation or charring]," she said.

The study was supported by the National Institutes of Health, the Stand Up To Cancer Colorectal Cancer Dream Team Translational Research Grant (coadministered by the American Association for Cancer Research), the Project P Fund, and others. The investigators, Dr. Wu, and Dr. Thompson-Carino reported no conflicts of interest related to this study.

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weight – the amount of weight patients needed to lose to reach normal BMI – compared with only 60.4% for ESG controls. Specifically, the mean percentage total body weight loss at the end of 12 months was 25.2% for those in the combination group, compared with 18.6% for those treated with ESG alone ($P < .001$).

Patients in the combination group lost 12.6% of their body fat mass, compared with 9% for ESG controls. Additionally, five patients in the combination group reverted to a nondiabetic state and were able to discontinue antidiabetic medications.

Dr. Hoff has reported no relevant financial relationships.

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Network meta-analysis ranks first-line *H. pylori* regimens

BY JIM KLING
MDedge News

A network meta-analysis of current first-line dual, triple, and quadruple therapies for *Helicobacter pylori* infection found that vonoprazan triple therapy was most effective, while standard triple therapy of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin was least effective (Turk J Gastroenterol. 2019 May;30[5]:420-35). Levofloxacin-containing triple therapy performed best in Western countries and West Asia, while reverse hybrid therapy was most effective in East Asia.

The results "[suggest that] a new approach concerning *H. pylori* treatment is now needed and that the time for transitioning from trial and error to antimicrobial stewardship [of *H. pylori* infection] has arrived," wrote Theodore Rokkas, PhD, MD, AGAF, of the European University of Cyprus in Engomi, and colleagues. Their study was published in Gastroenterology (2021. doi: 10.1053/j.gastro.2021.04.012).

H. pylori infection is the primary cause of gastritis, peptic ulcer disease, gastric mucosa–associated lymphoid tissue lymphoma, and gastric cancer.

Since *H. pylori* infection was first recognized, physicians have employed a range of drugs in double, triple, and quadruple combinations to combat it.

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In this perspective, the network meta-analysis by Rokkas and colleagues is very important: The purpose of this study is not only to identify those regimens with the highest treatment success in comparison but also stratify for world regions and time-shift aspects. The key value of the network approach, however, is the ability for indirect comparisons, as presented here. With use of the surface under the cumulative ranking values, vonoprazan-based triple therapy may be the most promising candidate for the future, non–bismuth quadruple and R-hybrid therapies are also suitable.

Dr. Treiber

So what is the take-home message from this paper? Unfortunately, the authors could not include data concerning drug dosage and resistance. I think that emphasizing the need for antibiotic stewardship on one hand and – at the same time – telling us to still rely on local resistance knowledge (whatever this means) is not enough in 2021. Our unit routinely monitors *Helicobacter pylori* resistance with a polymerase chain reaction technique in each single patient, revealing rates for resistance to macrolides and fluoroquinolones of around 20%. (Cost-effectiveness advice: Take only those biopsy specimens that have turned to be positive in the rapid urease test and send them in for polymerase chain reaction testing within 72 hours; 90% success.)

In this perspective, with currently sparse vonoprazan data limited to Japan, I still prefer to go primarily for the non–bismuth quadruple therapy (56 pills to be taken in 1 week), and from my own published data, this regimen will still work if taken for only 5 days. Vice versa, in the presence of macrolide resistance, amoxicillin allergy, previous treatment failures, I go for the bismuth quadruple therapy – if I can expect good treatment compliance because proton pump inhibitor plus potassium, metronidazole, and tetracycline for 10 days can mean 140 pills.

Gerhard G. Treiber, MD, AGAF, is with the department of internal medicine at Saarland University Hospital, Homburg, Germany. He has no conflicts of interest.

Tofacitinib in UC: Watch out for herpes zoster reactivation, thrombosis

BY JIM KLING
MDedge News

In a real-world test, tofacitinib had a similar safety profile to what was seen in clinical trials. The majority of adverse events seen were infections, and few were serious; however, the study did find evidence of rare venous thromboembolism (VTE) in patients with preexisting risk factors, which suggests that precaution is warranted in this group.

Tofacitinib, a Janus kinase inhibitor, was approved by the Food and Drug Administration in 2018 for adults with moderate to severe ulcerative colitis (UC). Three phase 3 clinical trials and an open-label, long-term extension trial found that the drug was associated with increased infection rates and higher lipid levels.

In rheumatoid arthritis patients, an interim analysis of a safety clinical trial of twice-daily doses of 10 mg tofacitinib showed increased rates of pulmonary embolism and all-cause mortality, compared to treatment with a dose of 5 mg or a tumor necrosis factor antagonist. That finding led to a boxed label warning against thrombosis. The current study, published in Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2020.06.050), included patients from six centers in the United States.

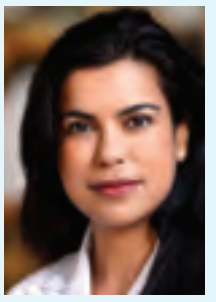
The findings suggest that patients should be counseled about the potential risk for herpes zoster (HZ) reactivation, especially older patients taking corticosteroids. The authors also recommended vaccination with an inactivated HZ vaccine.

The researchers followed 260 patients over a median of 6 months (median age, 38 years; 58.1% male; 71.9% non-Hispanic). Overall, 88.5% had previously received treatment with a biologic, most often an anti–tumor necrosis factor–alpha agent (76.5%). During follow-up, 15.7% experienced adverse events, most commonly infections (5.0%) and rash (3.5%). Joint pain (1.5%) and anemia (1.5%) also occurred. The incidence rate for any adverse event was 27.2 per 100 person-years. Adverse events occurred more often in older patients (mean age, 42 vs. 37 years; $P = .02$) and those who had not undergone previous anti-TNF therapy (63.4% vs 79.8%; $P = .03$). There was no association between concomitant steroid use and adverse events on univariate analysis. Of the overall cohort, 5.8% experienced a severe adverse event, with the most common being HZ rash (26.7% of severe adverse events). Therapy was discontinued by 4.6%.

Five patients developed HZ (3.29 per 100 person-years; 95% confidence interval, 1.37-7.90).

Continued on following page

Tofacitinib is an oral small molecule that received approval by the Food and Drug Administration in December 2019. To date, most safety data have been derived from clinical trials or past marketing registries. In this study, Deepak and colleagues report real-world data from a multicenter cohort.


Dr. Kaur

The study reported low rate of adverse events (15.7%) with the most common being infections and skin rashes. Interestingly, steroid use did not appear to increase risk of infections. Serious adverse events occurred in 5.8% and included two cases of venous thromboembolism (VTE). Most common infection was reactivation of herpes zoster virus (HZV). All cases occurred at the higher 10-mg twice-daily dosing and, with the exception of one patient, in HZV-unvaccinated individuals. These rates are similar to what have been previously reported from pooled safety data of phase 2 and 3 clinical trials of tofacitinib. Given these data, in my practice, I encourage all patients to receive the first dose of recombinant zoster vaccine before initiating tofacitinib.

The second adverse event of interest was VTE. The risk of VTE with tofacitinib first came to light in 2019 during an interim analysis of a safety trial in rheumatoid arthritis. The data prompted the FDA to issue a safety communication. In this study two patients developed VTE. Both were males on the 10-mg twice-daily dose. This number is a higher than expected for a cohort of this size and highlights the need for careful patient selection, risk-benefit discussion, close monitoring for signs of VTE, and early dose tapering when feasible.

In summary, most adverse effects related to tofacitinib can be mitigated with careful patient selection, pretreatment zoster vaccination, and timely dose taper.

Manreet Kaur, MD, medical director of Inflammatory Bowel Disease Center at Baylor College of Medicine, Houston. She has no conflicts of interest.

Continued from previous page

Despite those efforts, treatment success is lower than with many other infectious diseases. A newcomer is the potassium-competing acid blocker vonoprazan, which increases efficacy of amoxicillin combination therapies and has, thereby, generated renewed interest in all combination therapies, according to the study authors. Vonoprazan is currently available in some Asian countries, but not the United States or Europe.

Current guidelines for *H. pylori* treatment relied on randomized controlled trials and relevant pairwise meta-analyses, but no previous pairwise analysis has included all currently available medications, the authors noted. Network meta-analyses can help fill this evidence gap: They incorporate both direct and indirect evidence from a collection of randomized controlled trials to estimate the comparative effectiveness of three or more regimens.

The researchers conducted a network meta-analysis that included 68 randomized, controlled trials totaling 22,975 patients. The following regimens were included in the analysis: Concomitant quadruple bismuth treatment (bismuth quadruple therapy), concomitant quadruple nonbismuth treatment (nonbismuth quadruple therapy), high-dose amoxicillin double treatment (Amox-dual therapy), levofloxacin-containing treatment (Levo-therapy), reverse hybrid therapy (R-hybrid therapy), sequential quadruple treatment (sequential therapy), standard triple treatment (triple therapy), and vonoprazan-containing therapy (Vono-triple therapy).

Statistically significant results were found with Vono-triple therapy versus triple therapy (odds ratio, 3.80; 95% confidence interval, 1.62-8.94), sequential therapy versus triple therapy (OR, 1.79; 95% CI, 1.26-2.53), nonbismuth quadruple therapy versus triple therapy (OR, 2.08; 95% CI, 1.45-2.98), bismuth quadruple therapy versus triple therapy (OR, 1.47; 95% CI, 1.02-2.11), and Levo-therapy versus triple therapy (OR, 1.79; 95% CI, 1.26-2.53).

In the overall data, mean cure rates greater than 90% were seen only in Vono-triple therapy (91.4%; 95% CI, 88.5-93.5%) and R-hybrid therapy (93.6%; 95% CI, 90.4-96.8%). Cure rates were lower for Nonbismuth quadruple therapy (84.3%; 95% CI, 82.7-85.8%), Levo-therapy (83.8%; 95% CI, 82.1-85.4%), Sequential therapy (83.7%; 95% CI, 82.7-84.7%), bismuth quadruple therapy (81.3%; 95% CI, 79.5-83.1%), Amox-dual therapy (80.2%; 75.3%-84.4%), and triple therapy (75.7%; 95% CI, 74.9-76.4%). Levo-therapy performed best in Western countries (88.5%; 95% CI, 86.5-90.5%) and West Asia (88.4%; 95% CI, 84.6-91.1%). R-hybrid therapy performed best in East Asia (93.6%; 95% CI, 90.4-96.8%).

A surface under the cumulative ranking (SUCRA) value, which represents the efficacy of the intervention compared to an ideal intervention, was 92.4% for Vono-triple therapy. The second highest SUCRA value was for 68.8% for nonbismuth quadruple therapy. The SUCRA value of standard triple therapy was 4.7%.

A key limitation to the study is that Vono-triple therapy was tested only in Japan, and requires additional study in other geographic regions.

The study received support from the Department of Veteran Affairs. The authors have consulted for and received research funding from various pharmaceutical companies.

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Who's at risk for enterocolitis in Hirschsprung's?

BY JIM KLING
MDedge News

In a small study of Hirschsprung's disease (HSCR) patients, those with a low-fiber colonic mucosal acetylcholinesterase-positive (AChE+) innervation phenotype were more likely to suffer from postoperative enterocolitis, which can be life-threatening.

The study lends insight into crosstalk between the human enteric nervous and immune systems. It suggests a role for acetylcholine-secreting (cholinergic) nerve fibers in aganglionic sections of colon in patients with HSCR, which is a congenital disorder marked by the absence of enteric neuronal cells in the distal part of the gut.

There are also potential clinical implications. "These observations suggest that HSCR patients with low-fiber phenotype might have a higher risk of developing postoperative enterocolitis and that the fiber phenotype could serve as a predictive marker for development of prophylactic therapy," wrote Simone Keck, PhD, of the University of Basel (Switzerland) and colleagues in a study published in Cellular and Molecular Gastroenterology and Hepatology (2021 Mar 16;12[2]:507-45).

HSCR is a multigenetic congenital condition that includes a lack of enteric ganglia cells (aganglionosis) in the distal part of the colon, leading to intestinal obstruction and prestenotic megacolon. Treatment consists of pull-through surgery to remove the aganglionic portion of the bowel, but 20%-50% of patients develop life-threatening HSCR-associated enterocolitis before or after surgery. Although the mechanism of the complication is uncertain, immune cells, intestinal barrier function, and the microbiome may play a role.

Mouse models have shown connections between the immune and nervous system, but it has been challenging to study the effects of specific neurotransmitters in humans. There are more than 30 separate neurotransmitters in the enteric nervous system, making it difficult to tease apart individual functions. Because there are comparatively few enteric nervous system neurotransmitters in patients with HSCR and the aganglionic colon in these patients contains enlarged AChE+ nerve fibers, "neuronal cholinergic function can be examined particularly well" among these patients.

The researchers of the current study analyzed tissue from 44 pediatric HSCR patients who underwent pull-through surgery, along with 6 non-HSCR controls who had surgery for various other reasons. Tissue samples were semiquantitatively categorized according to the extent of colonic mucosal AChE+ innervation: Low-fiber rectosigmoid tissue lacked intrinsic nerve cell bodies and mucosal AChE+ innervation, while high-fiber tissue lacked nerve cell bodies but had mucosal AChE+ innervation. The researchers also determined tissue cytokine profile and immune cell frequencies, and used confocal immunofluorescence microscopy to determine proximity of macrophages to nerve fibers and 16S-rDNA sequencing to determine microbial populations.

They found that aganglionic low-fiber samples had higher levels of inflammatory cytokines. Levels of these cytokines were lower in both ganglionic sections of the colon and in high-fiber samples with mucosal AChE+ nerve fibers. Low-fiber samples also had elevated Th17 T cells, compared with high-fiber, aganglionic, and ganglionic distal colon samples.

Out of 42 patients, 9 developed enterocolitis within 1 year of surgery; 7 had a low-fiber phenotype, while 2 were high fiber. This difference was not statistically significant, but the researchers then performed a retrospective analysis of 29 HSCR patients to validate the findings. Of these, 14 developed enterocolitis after surgery, with 12 of the cases occurring among children with the low-fiber phenotype, and 2 cases occurred among those with the high-fiber phenotype.

The findings could help guide postsurgical management of HSCR by allowing clinicians to employ preventive measures against enterocolitis. Th17 cells are known to migrate to nearby mesenteric lymph nodes, where they may promote enterocolitis, and this site is usually not removed during HSCR surgery. Fiber phenotype could prompt a surgeon to also remove mesenteric lymph nodes to reduce enterocolitis risk.

The study was funded by the University of Basel. The authors have no relevant financial disclosures.

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Hirschsprung's disease is a hereditary childhood disorder in which the enteric nervous system develops abnormally in the distal bowel. As a consequence, peristalsis fails in the aganglionic segment, causing obstruction and prestenotic megacolon. Standard of care is the surgical removal of the affected part of the colon and the connection of healthy ganglionic tissue to the anus. Unfortunately, a large fraction of Hirschsprung's patients suffer from enterocolitis, diarrhea, and abdominal distention either before or after surgery, which can progress to life-threatening sepsis and organ failure.


Dr. Kaestner

In a prospective, multicenter study, Keck and colleagues analyzed colonic tissue recovered in the operating room to investigate the relationship between mucosal cholinergic innervation and enterocolitis in pediatric Hirschsprung's patients in unprecedented detail. This line of investigation was motivated by prior observations showing that cholinergic signals can prevent excessive inflammation in the colon by modulating the immune response to commensal microbes, which thus presents an example of neuroimmune crosstalk. Remarkably, the current study demonstrated that high levels of mucosal acetyl choline positive nerve fibers in the colon correlated with lower risk for postoperative enterocolitis. Intriguingly, determination of cholinergic fiber status in the colonic mucosa at time of surgery could thus become a new prognostic marker for the risk of postoperative enterocolitis in Hirschsprung's disease patients.

Further research is needed to determine the reason for different levels of cholinergic fibers in the aganglionic colon and to validate these findings in a separate patient cohort.

Klaus H. Kaestner, PhD, MS, is director of the Next Generation Sequencing Center at the University of Pennsylvania, Philadelphia. He has no conflicts of interest.

Continued from previous page

Risk factors for VTE were seen in 31.2% of the cohort, and two cases of VTE occurred during follow-up (1.32 per 100 person-years; 95% CI, 0.33-5.28), both in patients with extensive UC. There was no increased risk of complications following abdominal surgery. At baseline, 38.4% had an abnormal lipid profile, and this increased to 48.3% following 8 weeks of treatment.

Overall, 45% of patients were anemic at baseline. Females experienced a significant improvement by week 26 (median hemoglobin level, 13.0 g/dL; interquartile range, 12.5-13.8), while a similar improvement occurred by week 52 in males (median hemoglobin level, 13.6 g/dL; IQR, 12.57-14.0). At 52 weeks, the mean increase in hemoglobin was 5% (IQR, 0%-11.1%). The increase was greater in females (7.7%; IQR, 4.2%-11.7%) than in males (2.1%; IQR, –0.5% to 11.3%).

Limitations of the study include its retrospective nature and that the data-collection tools could have missed some adverse events because they were not adequately captured in the treating clinician's notes. However, the data trend similarly to a prospective study (Clin Gastroenterol Hepatol. 2020 Jan;18[1]:123-32.e3).

"In summary, we report safety signals on a real-world cohort of patients with UC initiated on tofacitinib in whom increasing age is a risk factor for [adverse events] and consistent with recent reports of a dose-dependent risk of HZ reactivation and VTE events in patients with a risk factor for VTE on the 10-mg twice-daily dosing," the authors concluded.

The study was funded by the American College of Gastroenterology, the Crohn's and Colitis Foundation, the Givin' it all for Guts Foundation, and the Lawrence C. Pakula, MD, Inflammatory Bowel Disease Research Innovation and Education Fund. The authors have financial ties with various pharmaceutical companies.

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Get to know 2021 award winners

David Y. Graham, MD

Dr. Graham is this year's recipient of the AGA William Beaumont Prize in Gastroenterology. A remarkable clinician, scientist, and mentor to the next generation of GI, Dr. Graham currently serves as professor of medicine-gastroenterology at Baylor College of Medicine in Houston.


Dr. Graham

Dr. Graham was born in Ancon, in the Panama Canal Zone, where his father was working as an engineer. The family eventually settled in Lake Jackson, a small gulf coast town outside of Houston. There he developed a love for outdoor activities including hunting, fishing, and riding horses. He received a bachelor's degree from the Notre Dame and returned home to Houston to receive his medical degree with honors from Baylor College of Medicine. Dr. Graham's training was interrupted by the Vietnam War, during which he was drafted into the U.S. Army as a flight surgeon.

In addition to his clinical and research missions, Dr. Graham has mentored numerous individuals during his years as a clinician scientist, many of whom have gone on to have successful careers in academic medicine. He has been an active AGA member for more than 4 decades, receiving several honors including the prestigious AGA Mentor Award in 2015 and the Janssen Award for Special Achievement in Gastroenterology.

Read more about Dr. Graham's life and contribution to the GI community in a commentary in Gastroenterology (2021 Jul;161[1]:333-5) written by Fasiha Kanwal, MD, and Hashem B. El-Serag, MD, MPH.

Kim E. Barrett, PhD, AGAF

Dr. Barrett is the 2021 recipient of the AGA Distinguished Achievement Award in Basic Science for her outstanding contributions to understanding mechanisms and regulation of intestinal epithelial transport and barrier function. She currently serves as distinguished professor of medicine at the University of California, San Diego, and is serving as a rotating appointment as director of the Division of Graduate Education of the National Science Foundation.


Dr. Barrett

Born in London, Dr. Barrett was the first of her family to attend college. She earned a BSc in Medicinal Chemistry at University College London where she also stayed to complete her PhD studies. After that, Dr. Barrett moved to the United States to continue her training at the National Institutes of Health and continued studying the functional heterogeneity of mast cells. She believes in having fun, living by the phrase "put yourself about a bit." She is a proud member of the band GI Distress as one of the "Fabulous Fasebettes."

Read more about Dr. Barrett's contributions to the GI community in a commentary in Gastroenterology (2021 Jul;161[1]:336-8), written by Mark Donowitz, MD, and Stephen Keely, MD.

Novel liver dialysis device may safely curb ACLF

BY NEIL OSTERWEIL
MDedge News

An investigational liver dialysis device (DIALIVE) was associated with significantly greater survival of patients with acute-on-chronic liver failure (ACLF), compared with the standard of care in a multicenter randomized study.

Among 30 evaluable patients with ACLF from alcoholic cirrhosis randomized to treatment with the DIALIVE system or standard of care, two-thirds of patients assigned to DIALIVE had both survived and experienced resolution of ACLF by 28 days, compared with one-third of patients assigned to standard of care, reported Banwari Agarwal, MBBS, MD, from the Royal Free Hospital in London at the meeting sponsored by the European Association for the Study of the Liver.

Different from MARS

The DIALIVE system differs from the Molecular Adsorbent Recirculating System (MARS) liver dialysis system in that DIALIVE removes and replaces albumin, including proinflammatory albumin, rather than filtering and recirculating it, he explained.

"It addresses systemic inflammation, which wasn't quite the case with MARS," he said in the question-and-answer portion of his presentation in a general session. In patients with ACLF, the risk of 28-day mortality increases substantially as the grade of ACLF increases.

"ACLF, however, is potentially reversible, and the initial grade at presentation undergoes changes over time during the natural course of the illness, with some patients deteriorating, some improving, and some even achieving complete ACLF resolution. The final grade is reached by days 3-7, and it is this final grade which determines their future outcome trajectory. I therefore propose that ACLF resolution in itself is an important therapeutic target," he said.

Study details

Dr. Agarwal and coinvestigators from eight centers in six European countries enrolled patients with a history indicative of alcohol-related cirrhosis, at least one acute decompensation event, and progression to ACLF grades 1, 2, or 3a.

Patients with an international normalized ratio above 3 were excluded, as were those with more than three organ failures, uncontrolled infections, primary respiratory organ failure, and hemodynamic instability refractory to volume resuscitation and low-dose vasopressors.

A total of 32 patients, of whom 30 were evaluable, were randomized to receive liver dialysis in three to five DIALIVE sessions lasting 8-12 hours each (15 evaluable patients) or to standard of care at participating institutions (15 patients).

> "It's very early, but we're really desperate in finding something to bridge to transplantation."

The investigators looked at safety of the device (the primary endpoint) in all patients who received at least one DIALIVE treatment (safety population), and a modified safety population of patients who received at least three DIALIVE treatments.

The median patient age in each arm was 49 years, and all patients had alcoholic cirrhosis, with alcoholic hepatitis accounting for at least one decompensation event. In addition, about 25% of patients in each arm had decompensation with infections and/or sepsis as precipitating factors.

Safety

Serious adverse events on days 1-10 occurred in 11 of 17 patients in the DIALIVE arm, and in 8 in the standard-of-care arm. In the DIALIVE arm, there were seven treatment-related serious device events, three unexpected serious device events (anemia, septic shock, and hypotension), and one patient discontinued dialysis after having unsafe levels of thrombocytopenia.

Four patients in the DIALIVE arm died on study. The first two died on day 1 one from hypotension, coagulopathy, and multiorgan failure, and this prompted a change in the protocol mandating that DIALIVE be conducted only in an ICU setting with more invasive monitoring and more frequent lab analysis of clotting and other biochemical parameters. Of the two other patients in the DIALIVE arm who died on study, one died from non-MI cardiac arrest on day 8, and one patient with ACLF grade 3 and a European Foundation for the study of chronic liver failure (CLIF)–ACLF score of 68 died from multiorgan failure.

"I must emphasize that even this very sick patient tolerated the device very, very well," Dr. Agarwal said.

In the standard-of-care arm, two patients died from progressive liver failure on days 17 and 27, respectively, and one died on day 17 from bacterial infections, bleeding, and progressive liver failure.

There were eight instances of filters clotting out of 64 filters used in total, and four episodes of device deficiency, including two instances where tubing could not be disconnected from an Oxiris filter during setup of the DIALIVE circuit, requiring use of new DIALIVE kits; one use of an incorrect dialysis fluid; and one incorrect setup of the DIALIVE circuit.

WIRATGASEM/GETTY IMAGES

Significant improvements in many scores

In the DIALIVE group, there were significant improvements over baseline at day 10 in both liver scores ($P < .05$) and brain scores ($P < .001$). In contrast, in the standard-of-care group there were no improvements in individual organ scores, and respiration scores were significantly worse ($P < .01$).

DIALIVE was also associated with significant improvements in CLIF-C organ failure scores, compared with standard of care at day 5 and day 10 ($P = .021$ and .001, respectively); CLIF-C–ACLF scores at days 5 and 10 ($P = .045$ and .023); and Model for End-Stage Liver Disease scores at day 5 ($P = .028$).

In the DIALIVE group, 40% of patients had ACLF resolution by day 5, and 66.7% had resolution by day 10. In the standard-of-care arm, 15% had resolution on day 5, and 33.3% had resolution on day 10. DIALIVE was also associated with a significantly faster median time to resolution, compared with standard of care (10 days vs. not reached; $P = .0307$). At 28 days, 10 of 15 evaluable patients were alive and had resolution of ACLF with DIALIVE versus 5 of 15 with standard of care ($P = .0281$).

Dr. Agarwal said that the data justify the implementation of late-phase clinical trials of the liver dialysis device.

'Hopeful' findings

"It's very early, but we're really desperate in finding something to bridge to transplantation," commented Tobias Boettler, MD, from the University of Freiburg (Germany), who was not involved in the study.

"I think this is very hopeful," said Dr. Boettler, who moderated the briefing where Dr. Agarwal summarized the study findings.

In the question and answer following the talk in a general session, moderator Philip N. Newsome, MD, from University Hospitals Birmingham (England) asked whether patients who were not treated should have been included in the analysis.

Dr. Agarwal replied that "the whole idea behind this study was to understand what this device does to these patients, and how these patients react to this device, so really not looking at the efficacy."

The study was supported by the European Union's Horizon 2020 initiative. Dr. Agarwal received a study grant from the initiative, but had no other relevant disclosures. Dr. Boettler and Dr. Newsome had no disclosures relevant to the study.

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Rapid HCV tests could expand accessibility

BY NEIL OSTERWEIL
MDedge News

A proposed rapid diagnostic test for hepatitis C viral infections that combines an inexpensive but lower-sensitivity core-antigen test with lab RNA confirmation of negative tests could expand testing and same-day initiation of antiviral therapy in places where resources are limited, investigators said.

Applying the proposed method to the Republic of Georgia, with a hepatitis C virus (HCV) prevalence of 5.4% as reported by the World Health Organization, would result in a 95.4% diagnosis rate, compared with 78.8% for lab-based RNA testing, which is the standard of care. Applied to Malaysia, the proposed method would boost diagnosis rates from 57.0% to 91.2%, reported Madeline Adee, MPH, from Massachusetts General Hospital's Institute for Technology Assessment in Boston and colleagues.

"We found that a novel core-antigen rapid diagnostic test for HCV could improve the diagnosis rate and result in cost savings. Although not yet developed, such a test could be a game changer and have a substantial impact on the feasibility and cost of HCV elimination, especially in low- and middle-income countries," they reported at EASD 2021, the meeting sponsored by the European Association for the Study of the Liver.

Although rapid tests for HCV can improve diagnosis and treatment rates, currently available molecular tests are expensive and require clinical laboratory infrastructure, which can put such tests out of the reach for clinicians in low- or middle-income countries. Rapid immunoassays based on HCV core antigens are cheaper, but their sensitivity ranges from 70% to 90%; in contrast, the third-generation HCV enzyme immunoassay has about a 98% sensitivity.

Could it work?

The proposed testing method would be likely to improve diagnosis, but whether that would translate into increased treatment is uncertain, commented Lesley Miller, MD, who specializes in HCV screening and treatment in underserved populations at Emory University, Atlanta.

"When we're talking about hepatitis C, it's all about the care cascade, the drop-off at each step from those who have the disease and aren't diagnosed, to those who are tested and only partially diagnosed because they don't have a confirmed infection, to those that get into care, get treated, and get cured," she said in an interview.

"It's all about closing the gaps in the care cascade in order to achieve elimination of the virus, which is what we're all trying to do," she said.

She pointed that there are certain at-risk populations in the United States, such as injectable-drug users, who might be able to benefit from such a system.

"These folks often have less access to traditional care, so bringing rapid testing and care to where those folks are is really important, so if we can deploy mobile units to areas where there is high prevalence and do it at the point of care, it simplifies the entire process," she said.

Thomas J. Hoerger, PhD, a senior fellow in health economics and financing at the nonprofit research group RTI International in Research Triangle Park, N.C., said in an interview that the proposed model could eliminate the step in testing in which patients are required to return for confirmation.

"People don't always come back for further testing, so if you can do it immediately and have the results of a screening test, you might be able to get people to come back more quickly. You still have the problem of the high cost of treatment, but this would at least make it a little more convenient," he said.

He noted that the success of the strategy would be dependent on the sensitivity of the rapid core-antigen test, it's cost relative to HCV RNA testing, and whether the availability of the rapid test would translate into an improvement in follow-up.

Neither Dr. Miller nor Dr. Hoerger were involved in the study.

Evaluating the approach

To determine whether a lower-cost rapid test could be cost effective, the researchers created a microsimulation model of the natural history of HCV to compare potential outcomes from either core-antigen rapid diagnostic testing with a base case sensitivity for HCV viremia of 80% with lab-based RNA confirmation for negative results or the current standard of care with lab-based RNA confirmation only.

The model incorporated METAVIR stage F0-F4, decompensated cirrhosis, hepatocellular carcinoma, and liver-related death. The investigators determined the baseline characteristics of HCV patients in each country based on different distributions of sex, HCV genotype, and METAVIR fibrosis stage.

They simulated outcomes for 10,000 adults in the Republic of Georgia, with an HCV prevalence of 5.4%, and Malaysia, with an HCV prevalence of 1.5%.

The model considers costs from a health care payer's perspective, and the investigations performed deterministic and probabilistic sensitivity analyses to evaluate how the cost-effectiveness of testing pathways might change when various factors were plugged into the model.

As noted before, the investigators determined that the core-antigen rapid test algorithm would improve diagnosis rates in Georgia from 78.8% to 95.4% and in Malaysia from 57.9% to 91.2%. The use of the rapid test would also increase quality-adjusted life-years in Georgia by 207 per 10,000 and in Malaysia by 146 per 10,000.

Cost savings, primarily from averting the costs of care for patients with HCV, begin within the first year of the model. Over 50 years, the lifetime horizon cost savings in Georgia would be $232,000 per 10,000 people, and the corresponding savings in Malaysia would be $504,000 per 10,000 people.

Even when allowing for variations in parameters, the core-antigen rapid diagnostic test approach remained the preferred model, the investigators reported.

The study was supported by the global health agency Unitaid. The researchers, Dr. Miller, and Dr. Hoerger reported no conflicts of interest relevant to the study.

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Patients with HIV/HCV see better transplant outcomes

BY ANDREW D. BOWSER
MDedge News

FROM DDW 2021

While liver transplant outcomes were historically poor in people coinfected with HIV and hepatitis C virus (HCV), they have improved significantly in the era of direct-acting antiviral (DAA) therapy, a recent analysis of U.S. organ transplant data showed.

The availability of highly potent DAA therapy should change how transplant specialists view patients coinfected with HIV/HCV who need a liver transplant, according to researcher Jennifer Wang, MD, chief gastroenterology fellow at the University of Chicago, who presented the results of the analysis at the annual Digestive Disease Week® (DDW). Cumulative graft survival rates since the introduction of DAAs are comparable between transplant recipients with HIV/HCV coinfection and recipients who are both HIV and HCV negative, according to the study.

"Having hepatitis C no longer confers worse patient survival in the DAA era, and this is the main takeaway from our study," Dr. Wang said.

Moreover, relatively few centers are performing liver transplants for patients who are HIV/HCV coinfected, and there is significant geographic variation in where the procedures are done, she said in her presentation.

Reassuring data that should prompt referral

Taken together, these results should offer reassurance to transplant centers that patients coinfected with HIV/HCV are no longer at increased risk for poor outcomes after transplantation, said Christine M. Durand, MD, associate professor of medicine at Johns Hopkins University, Baltimore.

"The additional call for action should be beyond the transplantation community to ensure that referrals for liver transplant are where they should be," Dr. Durand said in an interview.

"With a number of only 64 transplants a year, we're not doing enough, and there are more patients that could benefit from liver transplants," added Dr. Durand, who is principal investigator of HOPE in Action, a prospective, multicenter, clinical trial evaluating the safety and survival outcomes of HIV-positive deceased-donor liver transplants in HIV-positive recipients.

Impact of the HOPE Act, DAAs

Liver transplantation for HIV-positive patients has increased since the signing of the HIV Organ Policy Equity (HOPE) Act in 2013, according to Dr. Wang.

The HOPE Act expanded the donor pool to include HIV-positive deceased donors, which not only increased the donor supply overall, but specifically helped HIV-positive individuals, who experience a higher rate of waiting-list mortality, according to a review on the topic coauthored by Dr. Durand (Curr Opin Organ Transplant. 2018 Apr;23[2]:271-8).

However, some transplant centers may be reluctant to do liver transplants in HIV-positive patients coinfected with HCV. That's because, in previous studies that were conducted before the DAA era, outcomes after liver transplant in HIV/HCV-coinfected patients were inferior to those in patients with HIV but no HCV infection, Dr. Wang said.

Accordingly, Dr. Wang and colleagues analyzed Organ Procurement and Transplantation Network (OPTN) data on adult patients who underwent liver transplants between 2008 and 2019 to see if the introduction of DAAs had leveled the playing field for those with HCV coinfection.

Overall, out of 70,125 liver transplant recipients over the 2008-2019 period, 416 (0.6%) were HIV infected, the data show. In 2014, 28 liver transplants (0.5%) were performed in HIV-infected individuals, which increased to 64 transplants (0.8%) in 2019, data show. Of those 64 HIV-positive liver transplant recipients in 2019, 23 (35.9%) were coinfected with HCV. Graft survival has greatly improved, from a 3-year survival of only 58% in patients transplanted before the availability of DAAs to 82% in the DAA era, a difference that was statistically significant, Dr. Wang said.

Dr. Wang provided no financial disclosures related to the research. Dr. Durand disclosed financial relationships with AbbVie, GlaxoSmithKline, and Gilead Sciences.

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Safety-net burden linked with poorer inpatient cirrhosis outcomes

BY HEIDI SPLETE
MDedge News

Patients with cirrhosis treated at hospitals with the highest safety-net burden, defined by their proportion of Medicaid or uninsured patients, had a 5% higher mortality rate than patients who were treated at hospitals with the lowest burden, according to a study of over 300,000 patients.

The study, which was published in the Journal of Clinical Gastroenterology (2020 Oct. doi: 10.1097/MCG.0000000000001452), analyzed data from the National Inpatient Sample (NIS) database focusing on a 4-year time span between 2012 and 2016. The hospitals were categorized by safety-net burden, which was defined as having either a high, medium, or low number of uninsured patients or patients with Medicaid.

This is the first-known study to evaluate the impact of a hospital's safety-net burden on hospitalization outcomes in cirrhosis patients, wrote authors Robert J. Wong, MD, MS, of Stanford (Calif.) University and Grishma Hirode, MAS, of the University of Toronto. Previous studies have shown that safety-net hospitals, especially those with a high safety-net burden, have poorer patient outcomes. These hospitals also serve a patient population that is at high risk for chronic liver disease and cirrhosis.

The new analysis included 322,944 individual hospitalizations of patients with cirrhosis. In terms of safety-net burden, 107,446 hospitalizations were at high-burden hospitals, 103,508 were at medium-burden hospitals, and 111,990 hospitalizations were at low-burden hospitals.

Overall, cirrhosis-related hospitalizations in hospitals with the highest burden were found to have significantly greater odds of in-hospital mortality than the lowest-tertile hospitals (odds ratio, 1.05; $P = .044$). They also had a higher proportion of male patients, minority patients, Hispanic patients, and patients with Medicaid or no insurance.


Dr. Wong

The odds of hospitalization in the highest-tertile hospitals were found to be significantly higher, compared with the middle and lowest tertiles for Blacks and Hispanics, compared with Whites (OR, 1.26 and OR, 1.63, respectively). Black patients (OR, 1.26; 95% confidence interval, 1.17-1.35; $P < .001$) and Hispanic patients (OR, 1.63; 95% CI, 1.50-1.78; $P < .001$) were more likely to be admitted for care at high-burden hospitals (26%-54%).

"Despite adjusting for safety-net burden, our study continued to demonstrate ethnic disparities in in-hospital mortality among cirrhosis-related hospitalizations," the researchers wrote. Overall, the odds of in-hospital mortality were 27% higher in Black patients as compared with White patients.

However, significantly lower mortality was observed in Hispanic patients as compared with White patients (4.9% vs. 6.0%; $P < .001$), but why this occurred was not entirely clear. "Hispanic patients may be more likely to have NASH [nonalcoholic steatohepatitis]–related cirrhosis, which generally has a slower disease progression, compared with [hepatitis C virus] or alcoholic cirrhosis. As such, it is likely that NASH-cirrhosis Hispanic patients had less severe disease at presentation," the researchers wrote.

The study findings were limited by several factors including the inability to show causality based on the observational study design and cross-sectional nature of the database, the researchers said. The NIS database records individual hospitalizations, not individual patient data which means that it may include repeat hospitalizations from the same patient. In addition, the study was limited by a lack of data on outpatient cirrhosis outcomes and non–liver-related comorbidities.

The study received no outside funding. The researchers had no financial conflicts to disclose.

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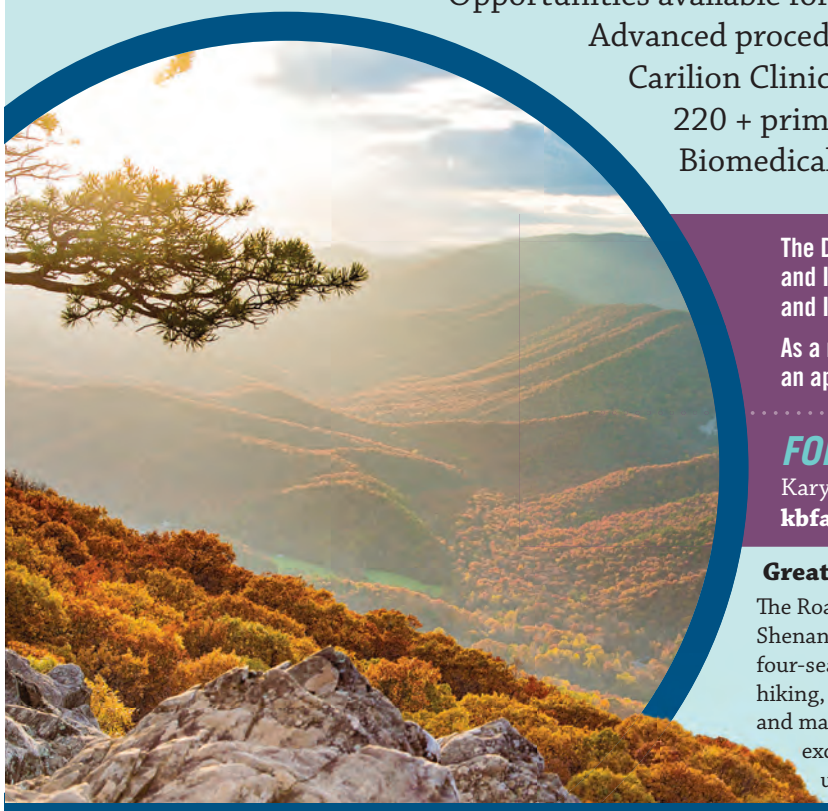

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Calories may outweigh nutrients in diets for fatty liver

BY LAIRD HARRISON

Intermittent calorie restriction offers only modest advantages over a low-carbohydrate, high-fat (LCHF) diet for treating nonalcoholic fatty liver disease (NAFLD), researchers say.

The intermittent diet offers more benefit for liver stiffness and LDL cholesterol, and might be easier to maintain, said Magnus Holmer, MD, head of the hepatology unit at the Karolinska Institute in Stockholm.

But the intermittent diet also has drawbacks and the differences between the two were slight, he said in an interview.

"They were more or less identically effective in reducing liver steatosis in NAFLD and also reducing body weight," he said. "And from this, we can say that the composition of macronutrients such as fat or sugar seems to be less important than how many calories you eat."

Dr. Holmer and colleagues presented their findings at the meeting sponsored by the European Association for the Study of the Liver and published them in JHEP Reports (2021 Feb 17. doi: 10.1016/j.jhepr.2021.100256).

While previous studies have shown that dieting can effectively treat NAFLD, researchers have debated whether popular LCHF diets might cause more harm than good.

At the same time, intermittent calorie restriction diets have also been gaining in popularity. Among the most popular is the 5:2 diet, in which participants eat normally for 5 days a week and restrict their calories significantly the other 2 days.

GERENME/THINKSTOCK

How do the two diets compare?

To see if one was more effective than the other, the researchers recruited 74 people with NAFLD. They diagnosed the patients either by radiologic assessment or a combination of controlled attenuation parameter (CAP) greater than 280 dB/m and obesity, or a CAP greater than 280 dB/m, elevated ALT, and overweight. Sixteen of the patients were being treated with statins.

The researchers randomly assigned 25 people to an LCHF diet, 25 to a 5:2 diet, and 24 to standard care. The groups were similar in diet, age, body mass index, liver stiffness, and most other criteria at baseline, although there were more women in the standard-care group.

At the start of the study, the participants in the standard-care group consulted with a hepatologist who advised them to avoid sweets and saturated fats, eat three meals a day, and avoid large portions.

The researchers asked women in the 5:2 diet to eat up to 500 kcal/day each of 2 days per week and up to 2,000 kcal/day each of the other 5 days. They asked men in the group to eat up to 600 kcal/day each of 2 days per week and up to 2,400 kcal/day the other 5 days.

They provided all the 5:2 participants with recipes that followed the Nordic Nutrition Recommendations, an adaptation of the Mediterranean diet that emphasizes foods traditional in Nordic countries, particularly grains such as whole-grain rye, oats, and barley; fruits such as apples, pears, berries, and plums; root vegetables, cabbages, onions, peas, beans, fish, boiled potatoes, and dairy products; and the use of rapeseed (canola) oil. The calories provided in the recipes were composed of 45%-60% carbohydrates, 25% fat, and 10%-20% protein.

The researchers asked women in the LCHF diet to eat an average of 1,600 kcal/day and men to eat an average of 1,900 kcal/day. All the participants used recipes based on meat, fish, eggs, low-carbohydrate vegetables, and dairy fat. Participants avoided sugar, bread, pasta, rice, pies, potatoes, and fruit. The calories in the recipes were composed of 5%-10% carbohydrates, 50%-80% fat, and 15%-40% protein.

All the participants reported what they ate over the previous 3 days, both at the start of the study and after 12 weeks. Participants in the 5:2 and LCHF groups also received follow-up calls to report their past 24 hours of eating at 2, 4, 8, and 12 weeks, and also at week 6, when they visited a dietitian.

In addition, the researchers measured the participants' linoleic acid and alpha-linolenic acid intake to verify that the participants' diets were different among the groups.

After 12 weeks, all three groups lost a significant amount of liver fat, but the LCHF and 5:2 groups lost more than the standard care group. Liver stiffness decreased significantly in the 5:2 and standard-care groups, but not in the LCHF group.

The differences in steatosis change between the standard-care and LCHF groups was statistically significant ($P = .001$), as it was between the standard-care and 5:2 groups ($P = .029$). The differences between the LCHF and 5:2 groups were not statistically significant for weight or steatosis, but they were statistically significant for liver stiffness.

In addition, the 5:2 group significantly reduced total and LDL cholesterol, while the standard-care group did not. In the LCHF group, levels of

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Digestive Diseases Self-Education Program

Quick Quiz answers

Q1. Correct answer: C. Esophagogastric junction outflow obstruction.

Rationale

Recent studies recognized the role of medications in inducing esophageal motor disorders. Opiates have been shown to be associated with esophagogastric junction outflow obstruction, achalasia (not type 1), and other hypercontractile esophageal abnormalities.

Reference

Camilleri M et al. Clin Gastroenterol Hepatol. 2017 Sep;15(9):1338-49.

Q2. Correct answer: A. CT scan.

Rationale

Given the change in bowel habits, colonoscopy in indicated to evaluate for inflammation. Anorectal manometry is helpful in evaluating sphincter function. Endoanal ultrasound can identify anal sphincter defects in the internal or external anal sphincter. Digital rectal exam is important in evaluating the anal area for skin tags, fissures, or scar. Digital exam can evaluate for resting anal sphincter tone and squeeze, pelvic floor descent, and strength of the pelvic floor muscles. CT is unlikely to contribute to the evaluation of a functional disorder.

Reference

Bharucha AE et al. Gastroenterology. 2006 Apr;130(5):1510-8.

Continued from previous page

LDL cholesterol, HDL cholesterol, and total cholesterol all increased.

The long-term implications of the cholesterol findings are unclear, Dr. Holmer said. He hopes to follow up on these patients after 18-24 months. But the initial cholesterol findings are perhaps enough to constitute a red flag for anyone with a history of cardiovascular disease.

Diet adherence

Only one person dropped out of the 5:2 group, compared with five in the LCHF group and four in the standard-care group. More people in the LCHF group reported adverse events, such as gastrointestinal upset.

"With LCHF, it's a drastic change for most people," Dr. Holmer said. "Many patients are a bit shocked when they realize how much fat they are supposed to eat for breakfast, for lunch, and for dinner. They might eat bacon and eggs for breakfast every day." The diet could be challenging for people who want to reduce their consumption of meat for environmental reasons.

The 5:2 group offers the advantage that people can choose what they want to eat as long as they adhere to the calorie restrictions, he pointed out. Still, he cautioned that the diet would not work well for people with insulin-dependent diabetes because of the difficulty of adjusting insulin levels on fasting days. He also recommended against this diet for people with cirrhosis because they need to eat frequent meals.

LCHF and 5:2 diets can work

But for most people the good news is that a variety of diets will work to treat NAFLD, Dr. Holmer said.

"I begin with saying to my patients that this can be completely cured, as long as you're able to lose weight," he said. "Then the next question is, how are they going to go ahead with that task? And if they're already interested in some sort of specific diet, then I can, based on these findings, encourage that."

Stephen Harrison, MD, a visiting professor of hepatology at Radcliffe Department of Medicine, University of Oxford (England), said that longer-term results will be important. For example, it will be interesting to see if the diets had effects on ballooning or inflammation.

Another limitation of the study is that it is relatively small in size, he said. He pointed out that people with NAFLD should increase their physical activity as well as eating less.

Still, Dr. Harrison greeted the findings enthusiastically, saying: "This is an important study."

It's useful to compare two popular diets head to head, and it's also encouraging to get confirmation that either one can work, he added.

The study was supported by grants from the Stockholm County Council, the Dietary Science Foundation (Kostfonden), the Skandia Research Foundation, and the Åke Wiberg Foundation. Dr. Holmer has disclosed no relevant financial relationships. Dr. Harrison is a consultant to Madrigal Pharmaceuticals.

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