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GI&Hepatology News

May 2022

Volume 16 / Number 5

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The practice update advises primary care providers to periodically review and document complaints that prompt PPI use.

AGA Clinical Practice Update: Expert Review

Deprescribing PPIs

BY JIM KLING
MDedge News

An American Gastroenterological Association practice update on deprescribing proton-pump inhibitors (PPIs) delineates conditions under which drug withdrawal should be considered, and acknowledges that conversations between physicians and patients can be complicated. An inappropriate decision to discontinue PPI therapy can have significant consequences for the patient, while continued inappropriate use raises health care costs and may rarely lead to adverse effects.

One purpose of the update is to provide guidance when patients and providers don't have the resources to systematically examine the issue, especially when other medical concerns may be in play. The authors also suggested that physicians include pharmacists in the employment of the best practices advice.

"None of these statements represents a radical departure from previously published guidance on PPI appropriateness and deprescribing: Our [recommendations] simply seek

See **PPIs** · *page 28*

New index predicts histologic remission for UC

Works well with artificial intelligence

BY MARCIA FRELLICK
MDedge News

A new score to gauge histologic remission in ulcerative colitis (UC), based simply on the presence or absence of neutrophils, is effective and easier to use than other indices, according to authors of a study published online in Gut (2022 Feb 16. doi: 10.1136/gutjnl-2021-326376).

Researchers, led by Xianyong Gui, MD, a surgical pathologist at the University of Washington, Seattle, developed the index, called the Paddington International Virtual Chromoendoscopy Score (PICaSSO) Histologic Remission Index (PHRI). They wrote that, when the index was plugged into an artificial intelligence (AI) model, the algorithm accurately determined histologic remission.

"Our preliminary AI algorithm differentiated active from quiescent UC with 78% sensitivity, 91.7% specificity, and 86% accuracy," the authors noted.

Histologic remission has been previously proposed as a treatment target for UC and many indices have been developed to score disease

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Will serrated polyp detection rates be the next CRC metric?

BY HEIDI SPLETE
MDedge News

A higher rate of serrated polyp detection was associated with a reduced risk of postcolonoscopy colorectal cancer, based on data from nearly 20,000 patients and 142 endoscopists, according to a study published in Gastrointestinal Endoscopy (2022 Mar 8. doi: 10.1016/j.gie.2022.03.001).

Higher rates of adenoma detection reduce the risk of postcolonoscopy colorectal cancer (PCCRC), but the data on detection rates for clinically significant serrated polyps and traditional serrated adenomas are

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INSIDE

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LETTER FROM THE EDITOR

San Diego, here we come

I attended my inaugural Digestive Disease Week® (DDW) in Orlando in 2013 as a first-year fellow, both excited and somewhat intimidated to be giving my first oral abstract presentation on an international stage. At that time, the only familiar faces at the conference were my co-fellows and faculty, along with a few welcoming faces from the fellowship interview trail. My attendings, on the other hand, couldn't walk more than 100 feet in the conference hall without bumping into a smiling colleague! Now nearly a decade later, I am pleased to say that there are many more familiar faces in the crowd as I walk the halls of DDW. Each May, I look forward to meeting up with friends and colleagues across the country and the world while learning from an outstanding group of GI thought-leaders. While the COVID pandemic has disrupted this annual tradition in recent years, for the first time since 2019 those who feel comfortable will convene in San Diego to see old colleagues and meet new ones, learn about exciting, practice-changing innovations in our field, and enjoy the California sunshine. For those who cannot travel, robust DDW virtual offerings are planned as well.

Dr. Adams

"Each May, I look forward to meeting up with friends and colleagues across the country and the world" at DDW.

A quick look at the 2022 conference schedule reveals an astonishing 3,300 oral abstract and poster presentations, 400 original lectures, and a variety of professional networking events on the agenda. The conference weekend will open with the AGA Post-Graduate Course, which offers a great opportunity to efficiently brush up on your clinical knowledge, guided by leading experts in the field. Monday, May 23, will feature the AGA Presidential Plenary, with AGA Institute President John M. Inadomi, MD, AGAF, and an exciting lineup of speakers discussing how best to address health care disparities impacting our patients and outlining AGA's recent efforts to promote diversity, equity, and inclusion in our field. While it is nearly impossible to attend all sessions of interest during this whirlwind 4-day conference, you can rely on GI & Hepatology News to bring you key conference highlights over the coming months to ensure you don't miss a beat!

Megan A. Adams, MD, JD, MSc
Editor in chief

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The AGA Institute headquarters is located at 4930 Del Ray Avenue, Bethesda, MD 20814, ginews@gastro.org.

GI & HEPATOLOGY NEWS (ISSN 1934-3450) is published monthly for $230.00 per year by Frontline Medical Communications Inc., 283-299 Market Street (2 Gateway Building), 4th Floor, Newark, NJ 07102. Phone 973-206-3434

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GI & HEPATOLOGY NEWS

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Crohn's: Guselkumab shows potential in phase 2 trial

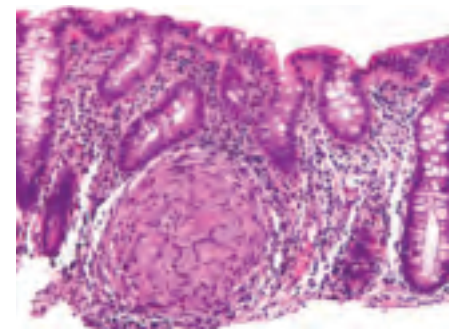
BY BRANDON MAY
MDedge News

Treatment with the human monoclonal antibody guselkumab over 12 weeks was shown to be safe and more effective than placebo in patients with moderate to severe Crohn's disease, according to phase 2 trial data

Conventional first-line therapies for Crohn's disease (CD) often are not effective for maintaining clinical remission and are associated with significant toxicity concerns, wrote study investigator William J. Sandborn, MD, AGAF, of the University of California, San Diego, and colleagues. Guselkumab is a human monoclonal antibody that selectively inhibits the p19 subunit of interleukin 23, a cytokine that plays an important role in gut inflammation, the researchers wrote. Their report was published online Feb. 5 in Gastroenterology (2022. doi: 10.1053/j.gastro.2022.01.047).

In the phase 2 GALAXI-1 study, Dr. Sandborn and colleagues evaluated the safety and efficacy of guselkumab in 309 patients with moderate to severe CD for at least 3 months. All patients previously had experienced either an inadequate response or intolerance to convention treatment or biologic agents.

Patients were randomly assigned to either placebo (n = 61); intravenous guselkumab at doses of 200 mg (n = 61), 600 mg (n = 63), or



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1,200 mg at weeks 0, 4, and 8 (n = 61); or a reference arm comprising ustekinumab approximately 6 mg/kg IV at week 0 and subcutaneous 90 mg at week 8 (n = 63).

The study's primary endpoint included the change from baseline to 12 weeks in the CD Activity Index score. The mean age of the population was 38.8 years and the mean duration of CD was 8.8 years.

There were patients in the primary efficacy analysis set who discontinued the study through week 12. At one point the study was paused to assess a serious adverse event of toxic hepatitis in a guselkumab-treated patient. Fifty-one patients were discontinued from the study because their induction treatment was paused during the adverse event evaluation; however, these patients were included in the safety analyses.

At the 12-week follow-up assessment, patients assigned to all doses of guselkumab experienced significantly greater reductions in

Continued on following page

Locoregional therapy lowers wait-list dropout in HCC

BY BRANDON MAY
MDedge News

The use of bridging locoregional therapy (LRT) before liver transplantation in patients with hepatocellular carcinoma (HCC) has significantly increased in the United States within the past 15 years, a recent analysis suggests. Data show that liver transplant candidates with HCC who have elevated tumor burden and patients with more compensated liver disease have received a greater number of treatments while awaiting transplant.

The researchers sought to examine the national temporal trends and wait-list outcomes of LRT in 31,609 patients eligible for liver transplant.

According to the researchers, led by Allison Kwong, MD, of Stanford (Calif.) University, liver transplant remains a curative option for individuals with unresectable HCC who meet prespecified size criteria. In the United States, a mandated waiting period of 6 months prior "to gaining exception points has been implemented" in an effort "to allow for consideration of tumor biology and reduce the disparities in wait-list dropout between HCC and non-HCC patients," the researchers wrote.

Several forms of LRT are now available for HCC, including chemoembolization, external beam radiation, radioembolization, and radiofrequency or microwave ablation. In the liver transplant setting, these LRT options enable management of intrahepatic disease in patients who are waiting for liver transplant, Dr. Kwong and colleagues explained.

The researchers, who published their study findings in the May issue of Clinical Gastroenterology and Hepatology (2021. doi: 10.1016/j.cgh.2021.07.048), sought to examine the national temporal trends and wait-list outcomes of LRT in 31,609 patients eligible for liver transplant with greater than or equal to one approved HCC exception application in the United States.

Patient data were obtained from the Organ Procurement and Transplantation Network

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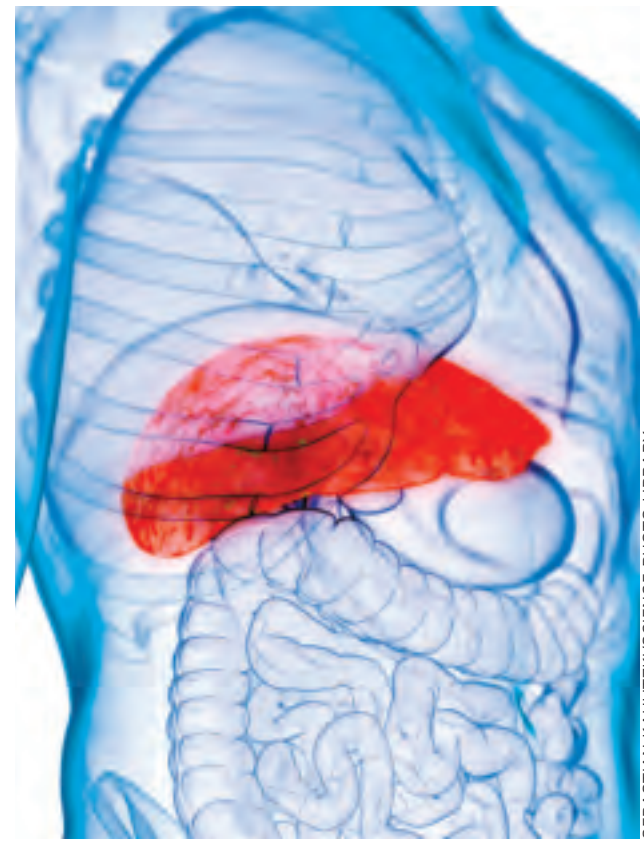

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the CD Activity Index from baseline when compared with placebo (least squares mean: 200 mg: –160.4; 600 mg: –138.9; and 1,200 mg: –144.9 vs. placebo: –36.2; all $P < .05$). In addition, a significantly greater proportion of patients in each guselkumab arm achieved clinical remission compared with the placebo group (CD Activity Index < 150; 57.4%, 55.6%, and 45.9% vs. 16.4%; all $P < .05$).

Among the patients who had an inadequate response or intolerance to prior biologic therapy, 47.5% of those in the combined guselkumab arm and 10.0% in the placebo arm met the criteria for clinical remission at 12 weeks. In addition, 62.4% of patients in the combined guselkumab group and 20% in the placebo group within the prior biologic therapy subgroup achieved clinical response at week 12.

Of patients with inadequate response or intolerance to prior conventional therapy, approximately 60% treated with guselkumab at all doses vs. 22.6% of the placebo group had clinical remission by 12 weeks. Also within this subgroup, 70.2% of patients in the combined guselkumab arm and 29% in the placebo arm had clinical response.

Finally, among the 360 patients in the safety analysis set, the proportions of patients with at least one adverse event were similar across the treatment groups during the treatment period (60% for placebo; 45.7% for guselkumab combined; 50.7% for ustekinumab).

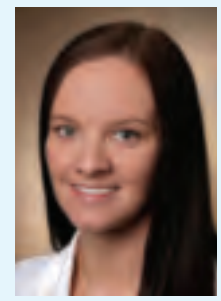
There was no observable relationship between the dose of guselkumab and the proportion of patients with adverse events. Infection rates were 21.4% in the placebo arm, 15.1% in the combined guselkumab group, and 12.7% in the ustekinumab arm. Approximately 3.7% of patients in the combined guselkumab arm, 5.7% of patients in the placebo arm, and 5.6% of patients in the ustekinumab arm experienced at least one serious adverse event.

Greater proportions of patients receiving guselkumab achieved clinical response, Patient Reported Outcomes–2 remission, clinical-biomarker response, and endoscopic response at week 12 vs. placebo. Efficacy of ustekinumab vs. placebo was demonstrated. Safety event rates were generally similar across treatment groups.

Limitations of the study included the small number of patients in the overall dataset and the relatively short treatment period of 12 weeks. The researchers noted that phase 3 studies of guselkumab for the treatment of Crohn's disease are underway.

Several of the researchers reported conflicts of interest with the pharmaceutical industry. The study received funding from Janssen Research & Development, LLC. ■

Over the last 20 years, multiple targeted therapies have been developed for Crohn's disease (CD) and have changed the management landscape for this chronic disease. Despite many successes, a proportion of patients still experience treatment failure or intolerance to the currently available biologics, and the need for ongoing development of new therapies remains. This study by Sandborn and colleagues highlights the development of a novel therapy for Crohn's disease patients. The novel therapy, guselkumab, targets a more specific interleukin pathway (IL-23p19 inhibition) than is currently available. In the study, guselkumab was found to be effective at improving multiple clinical parameters such as Crohn's Disease Activity Index and Patient-Reported Outcome–2 as well as objective parameters including biomarker response and endoscopic response in patients with moderate to severe CD. There was no apparent exposure response observed over multiple dose regimens. Guselkumab also demonstrated a favorable safety profile.



Dr. Dalal

As clinicians, the promising results from this phase 2 trial bring hope for additional treatment options for Crohn's disease patients. As the management landscape for CD further changes, options for patients will grow and thoughtful decisions regarding sequencing of the available therapies will become more important. More selective interleukin inhibition with IL-23p19 has been shown to be superior to dual blockade of IL-12/IL-23 in psoriasis; however, it is unknown if the same will be true for Crohn's disease. Further research will be needed in the future to address any potential efficacy and safety differences between the more specific target of IL-23 signaling.

Robin Dalal, MD, is an assistant professor of medicine, director of IBD education, and director of the advanced IBD fellowship at Vanderbilt University Medical Center in Nashville, Tenn. She reported being a consultant for AbbVie.

Researchers present cellular atlas of the human gut

BY BRANDON MAY
MDedge News

The investigators wrote that they hope their "database serves as a resource to understand how drugs affect the intestinal epithelium and as guidance for future precision medicine approaches."

New research sheds light on how different cell types behave across all intestinal regions and demonstrates variations in gene expression between these cells from duodenum to descending colon.

Research led by Joseph Burclaff, PhD, of the University of North Carolina at Chapel Hill, explained that the regional differences observed in the study "highlight the importance of regional selection when studying the gut." Dr. Burclaff and colleagues, whose findings were published online in Cellular and Molecular Gastroenterology and Hepatology (2022 Feb 14. doi: 10.1016/j.jcmgh.2022.02.007), wrote that they hope their "database serves as a resource to understand how drugs affect the intestinal epithelium and as guidance for future precision medicine approaches."

In the study, Dr. Burclaff and colleagues performed single-cell transcriptomics that covered the duodenum, jejunum, and ileum, as well as ascending, descending, and transverse colon from three independently processed organ donors. The donors varied in age, race, and body mass index.

The investigators evaluated 12,590 single epithelial cells for organ-specific lineage biomarkers, differentially regulated genes, receptors, and drug targets. The focus of the analyses was on intrinsic cell properties and their capacity for response to extrinsic signals that vary along the gut axis.

The research group assigned cells to 25 epithelial cell types. Remarkably, multiple accepted intestinal cell markers previously described in mice did not mark intestinal stem cells in humans. Additionally, the

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database and comprised primary adult LT candidates who were listed from the years 2003 to 2018. The investigators assessed explant histology and performed multivariable competing risk analysis to examine the relationship between the type of first LRT and time to wait-list dropout.

The wait-list dropout variable was defined by list removal because of death or excessive illness. The researchers noted that list removal likely represents disease progression "beyond transplantable criteria and beyond which patients were unlikely to benefit from or be eligible for further LRT."

In the study population, the median age was 59 years, and approximately 77% of patients were male. More than half (53.1%) of the cohort had hepatitis C as the predominant liver disease etiology. Patients had a median follow-up period of 214 days on the waiting list.

Most patients (79%) received deceased- or living-donor transplants, and 18.6% of patients were removed from the waiting list. Between the 2003 and 2006 period, the median wait-list time was 123 days, but this median wait-list duration increased to 257 days for patients listed between 2015 and 2018.

A total of 34,610 LRTs were performed among 24,145 liver transplant candidates during the study period. From 2003 to 2018, the proportion of patients with greater than or equal to 1 LRT recorded in the database rose from 42.3% to 92.4%, respectively. Most patients (67.8%) who received liver-directed therapy had a single LRT, while 23.8% of patients had two LRTs, 6.2% had three LRTs, and 2.2% had greater than or equal to four LRTs.

The most frequent type of LRT performed was chemoembolization, followed by thermal ablation. Radioembolization increased from less than 5% in 2013 to 19% in 2018. Moreover, in 2018, chemoembolization accounted for 50% of LRTs, while thermal ablation accounted for 22% of LRTs.

"Radioembolization and thermal ablation may be superior to chemoembolization and prove to be more cost-effective options, depending on the clinical context."

The incidence rates of LRT per 100 wait-list days was above average in patients who had an initial tumor burden beyond the Milan criteria (0.188), an alpha-fetoprotein level of 21-40 (0.171) or 41-500 ng/mL (0.179), Child-Pugh class A (0.160), and patients in short (0.151) and medium (0.154) wait-time regions, as well as patients who were listed following implementation of cap-and-delay in October 2015 (0.192).

In the multivariable competing-risk analysis for wait-list dropout, adjusting for initial tumor burden and AFP, Child-Pugh class, wait region, and listing era, no locoregional therapy was associated with an increased risk of wait-list dropout versus chemoembolization as the first LRT in a multivariable competing-risk analysis (subhazard ratio, 1.37; 95% confidence interval, 1.28-1.47). The inverse probability of treatment weighting–adjusted analysis found an association between radioembolization, when compared with chemoembolization, and a reduced risk of wait-list dropout (sHR, 0.85; 95% CI, 0.81-0.89). Thermal ablation was also associated with a reduced risk of wait-list dropout, compared with chemoembolization (sHR, 0.95; 95% CI, 0.91-0.99). "Radioembolization and thermal ablation may be superior to chemoembolization and prove to be more cost-effective options, depending on the clinical context," the researchers wrote.

The researchers noted that they were unable to distinguish patients who were removed from the waiting list between those with disease progression versus liver failure.

The researchers reported no conflicts of interest with the pharmaceutical industry. The study received no industry funding. ■

In 1996, Mazzaferro and colleagues reported the results of a cohort of 48 patients with cirrhosis who had small, unresectable hepatocellular carcinoma (HCC). The actuarial survival rate was 75% at 4 years, and 83% of these patients had no recurrence, so, orthotopic liver transplantation became one of the standard options with curative intent for the treatment HCC. Because of HCC biology, some of these tumors grow or, worst-case scenario, are outside the Milan criteria. Locoregional therapies (LRT) were applied to arrest or downsize the tumor(s) to be within the liver transplantation criteria.


Dr. Hernaez

Kwong and colleagues, using the data of the Organ Procurement and Transplantation Network database, showed an exponential increase of LRT over 15 years: from 32.5% in 2003 to 92.4% in 2018. The Barcelona Clinic Liver Cancer staging system classifies chemoembolization, the most common LRT modality used in this cohort, as a palliative treatment rather than curative.

Not surprisingly, the authors found that radioembolization was independently associated with a 15% reduction in the wait-list dropout rate, compared with chemoembolization. Further, listing in longer wait-time regions and more recent years was independently associated with a higher likelihood of wait-list dropout.

These data may be worrisome for patients listed for HCC. The median Model for End-Stage Liver Disease at Transplant Minus 3 National Policy, introduced in May 2019, decreases the transplantation rates in patients with HCC. Consequently, longer wait-list time leads to increase utilization of LRT to keep these patients within criteria. Radioembolization could become the preferred LRT therapy to stop tumor growth than chemoembolization and, probably, will be more cost effective. Future work should address explant outcomes and outcome on downstaging with external radiation therapy and adjuvant use of immunotherapy.

Ruben Hernaez, MD, MPH, PhD, is an assistant professor at the Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, both in Houston. He has no relevant conflicts to disclose.

Continued from previous page

investigators explained that lysozyme expression – previously used as the definitive Paneth cell marker, is insufficient for defining human Paneth cells. Even more importantly, they document that Paneth cells, previously suggested to function as the intestinal stem cell niche, do not produce any of the growth factors and signaling molecules required to promote stem cell proliferation.

Bestrophin-4þ (BEST4þ) cells, which express neuropeptide Y, demonstrated maturational differences between the colon and small intestine, suggesting organ-specific maturation for this recently discovered human specific cell type. In addition, the data from Dr. Burclaff and colleagues suggest BEST4+ cells are engaged in "diverse roles within the intestinal epithelium, laying the groundwork for functional studies."

The researchers noted that "tuft cells possess a broad ability to interact with the innate and adaptive immune systems through previously unreported receptors." Specifically, the researchers found these cells activate genes believed to be important for taste signaling, monitoring intestinal content, and signaling the immune system.

Certain classes of cell junctions, hormones, mucins, and nutrient absorption genes demonstrated "unappreciated regional expression differences across lineages," the researchers wrote. The investigators added that the differential expression of receptors as well as drug targets across lineages demonstrated "biological variation and the potential for variegated responses."

The researchers noted that, while the regional differences identified in their study show the importance of regional selection during gut investigations, several previous colonic single-cell RNA-sequencing studies did not specify the sample region or explain "if pooled samples are from consistent regions."

In the study, the investigators also assessed how drugs may affect the intestinal epithelium and why certain side effects associated with pharmacologic agents occur. The researchers identified 498 drugs approved by the Food and Drug Administration that had 232 primary gene targets expressed in gut epithelial cells.

In their analysis, the researchers found that carboxylesterase-2, which metabolizes the drug irinotecan into biologically active SN-38, is the most highly expressed phase 1 metabolism gene in the small intestine. The phase 2 enzyme UGT1A1, which inactivates SN-38, features low gut epithelial expression. The researchers explained that this finding suggests that the cancer drug irinotecan may feature prolonged gut activation, supporting the notion that the orally administered agent may have efficacy against cancers of the intestine.

The researchers concluded their "database provides a foundation for understanding individual contributions of diverse epithelial cells across the length of the human intestine and colon to maintain physiologic function."

The researchers reported no conflicts of interest with the pharmaceutical industry. The study received no industry funding. ■

Sebastian Kaulitzki/Science Photo Library/Getty Images

Single-cell transcriptomics has revolutionized our understanding of complex tissues, as this technology enables the identification of rare and/or novel cell types. Gastrointestinal science has benefited greatly from these technical advances, with multiple studies profiling liver, pancreas, stomach and intestine in health and disease, both in mouse and human samples.

Dr. Kaestner

The study by Burclaff and colleagues recently published in Cellular and Molecular Gastroenterology and Hepatology is the most comprehensive analysis of the healthy human intestine to date, profiling over 12,000 single epithelial cells from three donors along the anterior-posterior axis from duodenum to descending colon. In a truly monumental work covering 35 journal pages, the authors not only delineate in great detail the various cell lineages – from stem cell to full differentiated enterocyte, for instance – but also make surprising discoveries that will change our thinking about fundamental issues in gastrointestinal biology.

For instance, they find that human small intestinal Paneth cells, known for the production of antimicrobial peptides and long thought to be a critical component of the intestinal stem cell niche, do not express any of the niche factors, including mitogens such as epidermal growth factor, that had been attributed to Paneth cells in mice. The authors conclude that human Paneth cells are not major niche-supporting cells, in keeping with the recent identification of subepithelial telocytes as the critical cells that support crypt proliferation in mice. In addition, the authors' analysis of so called "BEST4" cells, an intestinal lineage absent from the mouse gut, suggests a novel function for this rare cell type in metal absorption.

In sum, this study is the "final answer" for GI biologists needing a complete compendium of all genes active in the multitude of specialized human intestinal epithelial cells.

Klaus H. Kaestner, PhD, MS, is with the department of genetics and the Center for Molecular Studies in Digestive and Liver Diseases at the University of Pennsylvania, Philadelphia. He declares having no conflicts of interest.

PIXELPERFECTSTOCK/THINKSTOCK

An aspirin a day to keep ... CRC away?

Dear colleagues,
We are all often asked by friends, colleagues, and especially patients how to reduce the risk of getting colorectal cancer. We offer exercise, diet, and smoking cessation as some possible ways to mitigate risk. But what about that wonder drug – the ubiquitous aspirin? The American Gastroenterological Association's recent clinical practice update suggests that aspirin may be protective in some patients younger than 70 years depending on their cardiovascular and gastrointestinal bleeding risks. If so, should we gastroenterologists be the ones to recommend or even prescribe aspirin? Or are the data just not there yet? We invite two colorectal cancer experts, Dr. Sonia Kupfer and Dr. Jennifer Weiss, to share their perspectives in light of these new recommendations. I invite you to a great debate and look forward to hearing your own thoughts online and by email at ginews@gastro.org.

Dr. Ketwaroo

Gyanprakash A. Ketwaroo, MD, MSc, is assistant professor of medicine at Baylor College of Medicine, Houston. He is an associate editor for GI & Hepatology News.

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Yes, but individualize it

Colorectal cancer (CRC) is one of the top three causes of cancer and cancer death worldwide with an alarming rise in younger adults. Preventive strategies including screening, chemoprevention, and risk factor modification are important to reduce overall CRC burden. Aspirin, which is cheap and readily available, is supported for CRC chemoprevention by multiple lines of strong evidence. Recent AGA practice guidelines recommend low-dose aspirin chemoprevention in individuals at average CRC risk who are younger than 70 years with a life expectancy of at least 10 years, have a 10-year cardiovascular disease risk of at least 10% and are not at high risk for bleeding. This advice diverges from the most recent U.S. Preventive Services Task Force–proposed guidelines that reverse the 2016 USPSTF recommendation for aspirin CRC chemoprevention (and primary prevention of cardiovascular disease) based on uncertainty of net benefit over harms especially in older individuals. In light of conflicting advice, how should we counsel our patients about aspirin use for CRC chemoprevention? In my opinion, we shouldn't "throw the baby out with the bathwater" and should follow the AGA practice guideline to individualize aspirin chemoprevention based on balancing known benefits and risks.

Dr. Kupfer

Sonia Kupfer, MD, AGAF, is an associate professor of medicine, director of the Gastrointestinal Cancer Risk and Prevention Clinic, and codirector of Comprehensive Cancer Risk and Prevention Clinic at the University of Chicago. She has no conflicts.

Not our lane

In 2021, the AGA published a clinical practice update on chemoprevention for colorectal neoplasia that advises clinicians to use low-dose aspirin to reduce colorectal cancer (CRC) incidence and mortality in average-risk individuals who are (1) younger than 70 years with a life expectancy of at least 10 years, (2) have at least a 10% 10-year cardiovascular disease (CVD) risk, and (3) are not at high risk for gastrointestinal bleeding. As gastroenterologists, we may see average-risk patients only at the time of their screening or surveillance colonoscopies, and I wonder if we should be taking the lead in prescribing/recommending aspirin for CRC chemoprevention in these patients. To answer this question, I will review three main concerns: (1) issues with the overall strength of the evidence on the effectiveness of aspirin to reduce CRC incidence and mortality, (2) determining an individual's long-term CVD risk and life expectancy may be outside of a gastroenterologist's purview, and (3) the potential for serious gastrointestinal bleeding is dynamic and requires continual review.

Dr. Weiss

Jennifer Weiss, MD, MS, AGAF, is an associate professor in the division of gastroenterology and hepatology and director of University of Wisconsin Gastroenterology Genetics Clinic at University of Wisconsin School of Medicine and Public Health, Madison. She reports receiving research support from Exact Sciences as a site–principal investigator of a multi-site trial.

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Management of gastroparesis in 2022

In Focus
Brought To You By The New Gastroenterologist

BY PRATEEK MATHUR, MD, AND THOMAS L. ABELL, MD

Introduction

Patients presenting with the symptoms of gastroparesis (Gp) are commonly seen in gastroenterology practice. This article reviews the presentation, pathophysiology, diagnosis, and treatment of gastroparesis syndromes with an emphasis on newer approaches evolving in clinical practice.

Presentation

Patients with foregut symptoms of Gp have characteristic presentations, with nausea, vomiting/retching, and abdominal pain often associated with bloating and distension, early satiety, anorexia, and heartburn. Mid- and hindgut gastrointestinal and/or urinary symptoms may be seen in patients with Gp as well.

The precise epidemiology of gastroparesis syndromes (GpS) is unknown. Classic gastroparesis, defined as delayed gastric emptying without known mechanical obstruction, has a prevalence of about 10 per 100,000 population in men and 30 per 100,000 in women with women being affected 3-4 times more than men.[1,2] Some risk factors for GpS, such as diabetes mellitus (DM) in up to 5% of patients with Type 1 DM, are known.[3] White individuals have the highest prevalence of GpS, followed by African Americans.[4,5]

The classic definition of Gp has blurred with the realization that patients may have symptoms of Gp without delayed solid gastric emptying. Some patients have been described as having chronic unexplained nausea and vomiting or gastroparesis-like syndrome.[6] More recently the National Institutes of Health Gastroparesis Consortium has proposed that disorders like functional dyspepsia may be a spectrum of the two disorders and classic Gp.[7] With use of this broadened definition, the number of patients with Gp symptoms is much greater, found in 10% or more of the U.S. population.[8] For this discussion, GpS is used to encompass this spectrum of disorders.

The etiology of GpS is often unknown for a given patient, but clues to etiology exist in what is known about pathophysiology. Types of Gp are described as being idiopathic, diabetic, or postsurgical, each of which may have varying pathophysiology. Many patients with mild to moderate GpS symptoms are effectively treated with outpatient therapies; other patients may be refractory to available treatments. Refractory GpS patients have a high burden of illness affecting them, their families, providers, hospitals, and payers.

Pathophysiology

Specific types of gastroparesis syndromes have variable pathophysiology (Figure 1). In some cases, like GpS associated with DM, pathophysiology is partially related to diabetic autonomic dysfunction. GpS are multifactorial, however, and rather than focusing on subtypes, this discussion focuses on shared pathophysiology. Understanding pathophysiology is key to determining treatment options and potential future targets for therapy.

Intragastric mechanical dysfunction, both proximal (fundic relaxation and accommodation and/or lack of fundic contractility) and distal stomach (antral hypomotility) may be involved. Additionally, intragastric electrical disturbances in frequency, amplitude, and propagation of gastric electrical waves can be seen with low/high-resolution gastric mapping.

Both gastroesophageal and gastropyloric sphincter dysfunction may be seen. Esophageal dysfunction is frequently seen but is not always categorized in GpS. Pyloric dysfunction is increasingly a focus of both diagnosis and therapy. GI anatomic abnormalities can be identified with gastric biopsies of full-thickness muscle and mucosa. CD117/interstitial cells of Cajal, neural fibers, and inflammatory and other cells can be evaluated by light microscopy, electron microscopy, and special staining techniques.

Small-bowel, mid-, and hindgut dysmotility involvement has often been associated with pathologies of intragastric motility. Not only GI but genitourinary dysfunction may be associated with fore- and midgut dysfunction in GpS. Equally well described are abnormalities of the autonomic and sensory nervous system, which have recently been better quantified. Serologic measures, such as channelopathies and other antibody-mediated abnormalities, have been recently noted.

Suspected for many years, immune dysregulation has now been documented in patients with GpS. Further investigation, including genetic dysregulation of immune measures, is ongoing. Other mechanisms include systemic and local inflammation, hormonal abnormalities, macro- and micronutrient deficiencies, dysregulation in GI microbiome, and physical frailty. The above factors may play a role in the pathophysiology of GpS, and it is likely that many of these are involved with a given patient presenting for care.[9]

Diagnosis of GpS

Diagnosis of GpS is often delayed and can be challenging; various tools have been developed, but not all are used. A diagnostic approach for patients with symptoms of Gp is listed below, and Figure 2 details a diagnostic approach and treatment options for symptomatic patients.

Symptom Assessment: Initially Gp symptoms can be assessed using Food and Drug Administration–approved patient-reported outcomes, including frequency and severity of nausea, vomiting, anorexia/early satiety, bloating/distention, and abdominal pain on a 0-4, 0-5, or 0-10 scale. The Gastrointestinal Cardinal Symptom Index or visual analog

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Gastroparesis is classically defined as delayed gastric emptying in the absence of mechanical obstruction in conjunction with nausea, vomiting, or early satiety. Gastroparesis occurs as the sequelae of diabetes, viral syndromes, or surgery, but it may be idiopathic as well. The mainstay of initial management is dietary modification, whereas the use of prokinetics is often limited by adverse effect profiles and varying degrees of efficacy, which poses a therapeutic challenge to the gastroenterologist.

The In Focus article for May, which is brought to you by The New Gastroenterologist, provides a detailed review of the diagnosis and management of gastroparesis syndromes. Dr. Thomas L. Abell and Dr. Prateek Mathur (University of Louisville [Ky.]) offer a comprehensive discussion of the utility and efficacy of dietary modifications, medications, pylorus-directed therapies, bioelectric therapy, and other novel approaches to treatment.

Vijaya L. Rao, MD
Editor in Chief
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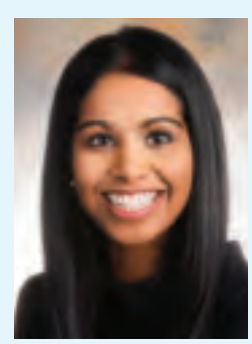

scales can also be used. It is also important to evaluate midgut and hindgut symptoms.[9-11]

Mechanical obstruction assessment: Mechanical obstruction can be ruled out using upper endoscopy or barium studies.

Physiologic testing: The most common is radionuclide gastric emptying testing (GET). Compliance with guidelines, standardization, and consistency of GETs is vital to help with an accurate diagnosis. Currently, two consensus recommendations for the standardized performance of GETs exist.[12,13] Breath testing is FDA approved in the United States and can be used as an alternative. Wireless motility capsule testing can be complementary.

Gastric dysrhythmias assessment: Assessment of gastric dysrhythmias can be performed in outpatient settings using cutaneous electrogastrogram, currently available in many referral centers. Most patients with GpS have an underlying gastric electrical abnormality.[14,15]

Sphincter dysfunction assessment: Both proximal and distal sphincter abnormalities have been described for many years and are of particular interest recently. Use of the functional luminal imaging probe (FLIP) shows patients with GpS may have decreased sphincter distensibility when examining the comparisons of the cross-sectional area relative to pressure. With use of this information, sphincter therapies can be offered.[16-18]

Other testing: Neurologic and autonomic testing, along with psychosocial, genetic, and frailty assessments, are helpful to explore.[19] Nutritional evaluation can be done using standardized scales, such as subjective global assessment and serologic testing for micronutrient deficiency or electrical impedance.[20]

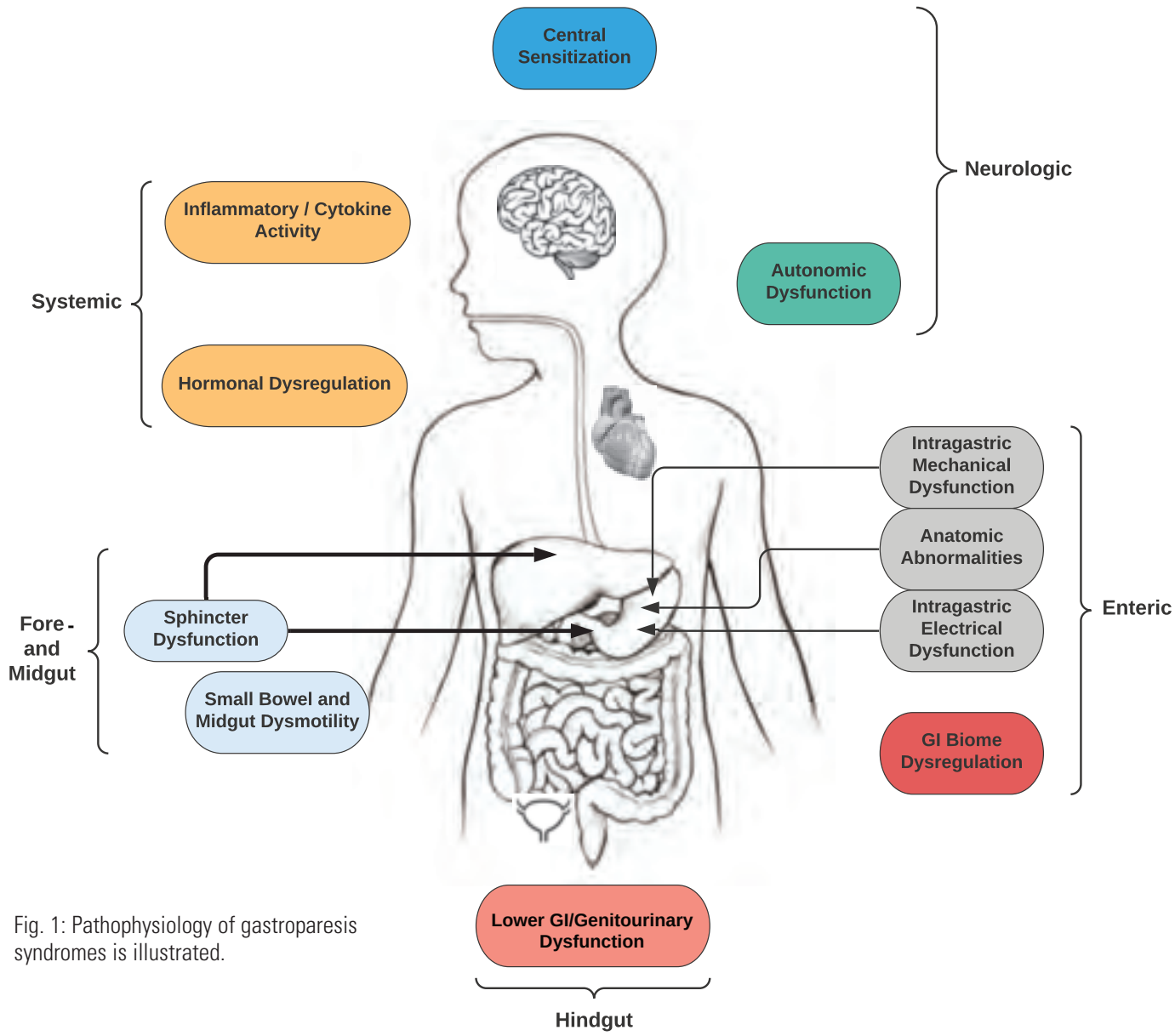

Fig. 1: Pathophysiology of gastroparesis syndromes is illustrated.

Dr. Pratee K Mathur and Dr. Thomas L. Abell

Treatment of GpS

Therapies for GpS can be viewed as the five **D's: Diet, Drug, Disruption, Devices, and Details**.

Diet and nutrition: The mainstay treatment of GpS remains **dietary** modification. The most common recommendation is to limit meal size, often with increased meal frequency, as well as nutrient composition, in areas that may retard gastric emptying. In addition, some patients with GpS report intolerances of specific foods, such as specific carbohydrates. Nutritional consultation can assist patients with meals tailored for their current nutritional needs. Nutritional supplementation is widely used for patients with GpS.[20]

Pharmacological treatment: The next tier of treatment for GpS is **drugs**. Review of a patient's medications is important to minimize drugs that may retard gastric emptying such as opiates and GLP-1 agonists. A full discussion of medications is beyond the scope of this article, but classes of drugs available include: prokinetics, antiemetics, neuromodulators, and investigational agents.

There is only one approved prokinetic medication for gastroparesis – the dopamine blocker metoclopramide – and most providers are aware of metoclopramide's limitations in terms of potential side effects, such as the risk of tardive dyskinesia and labeling on duration of therapy, with a maximum of 12 weeks recommended. Alternative prokinetics, such as domperidone, are not easily available in the United States; some mediations approved for other indications, such as the 5-HT drug prucalopride, are sometimes given for GpS off-label. Antiemetics such as promethazine and ondansetron are frequently used for symptomatic control in GpS. Despite lack of positive controlled trials in Gp, neuromodulator drugs, such as tricyclic or tetracyclic antidepressants like amitriptyline or mirtazapine are often used; their efficacy is more proven in the functional dyspepsia area. Other drugs such as the NK-1 drug aprepitant have been studied in Gp and are sometimes used off-label. Drugs such as scopolamine and related compounds can also provide symptomatic relief, as can the tetrahydrocannabinol-containing drug, dronabinol. New pharmacologic agents for GpS include investigational drugs such as ghrelin agonists and several novel compounds, none of which are currently FDA approved.[21,22]

Fortunately, the majority of patients with GpS respond to conservative therapies, such as dietary changes and/or medications. The last part of the section on treatment of GpS includes patients that are diet and drug refractory. Patients in this group are often referred to gastroenterologists and can be complex, time consuming, and frustrating to provide care for. Many of these patients are eventually seen in referral centers, and some travel great distances and have considerable medical expenses.

Pylorus-directed therapies: The recent renewed interest in pyloric dysfunction in patients with Gp symptoms has led to a great deal of clinical activity. Gastropyloric dysfunction in Gp has been documented for decades, originally in diabetic patients with autonomic and enteric neuropathy. The use of botulinum toxin in upper- and lower-gastric sphincters has led to continuing use of this therapy for patients with GpS. Despite initial negative controlled trials of botulinum toxin in the pyloric sphincter, newer studies indicate that physiologic measures, such as the FLIP, may help with patient selection. Other **disruptive** pyloric therapies, including pyloromyotomy, per oral pyloromyotomy, and gastric peroral endoscopic myotomy, are supported by open-label use, despite a lack of published positive controlled trials.[17]

Bioelectric therapy: Another approach for patients with symptomatic drug refractory GpS is bioelectric device therapies, which can be delivered several ways, including directly to the stomach or to the spinal cord or the vagus nerve in the neck or ear, as well as by electro-acupuncture.

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High-frequency, low-energy gastric electrical stimulation (GES) is the best studied. First done in 1992 as an experimental therapy, GES was investigational from 1995 to 2000, when it became FDA approved as a humanitarian-use device. GES has been used in over 10,000 patients worldwide; only a small number (greater than 700 study patients) have been in controlled trials. Nine controlled trials of GES have been primarily positive, and durability for over 10 years has been shown. Temporary GES can also be performed endoscopically, although that is an off-label procedure. It has been shown to predict long-term therapy outcome.[23-26]

Nutritional support: Nutritional abnormalities in some cases of GpS lead to consideration of enteral tubes, starting with a trial of feeding with an N-J tube placed endoscopically. An N-J trial is most often performed in patients who have macro-malnutrition and weight loss but can be considered for other highly symptomatic patients. Other endoscopic tubes can be PEG or PEG-J or direct PEJ tubes. Some patients may require surgical placement of enteral tubes, presenting an opportunity for a small-bowel or gastric full -hickness biopsy. Enteral tubes are sometimes used for decompression in highly symptomatic patients.[27]

For patients presenting with neurological symptoms, findings and serologic abnormalities have led to interest in immunotherapies. One is intravenous immunoglobulin, given parenterally. Several open-label studies have been published, the most recent one with 47 patients showing better response if glutamic acid decarboxylase–65 antibodies were present and with longer therapeutic dosing.[28] Drawbacks to immunotherapies like intravenous immunoglobulin are costly and require parenteral access.

Other evaluation/treatments for drug-refractory patients can be **detailed** as follows: First, an overall quality of life assessment can be helpful, especially one that includes impact of GpS on the patients and family. Nutritional considerations, which may not have been fully assessed, can be examined in more detail. Frailty assessments may show the need for physical therapy. Assessment for home care needs may indicate, in severe patients, needs for IV fluids at home, either enteral or parenteral, if nutrition is not adequate. Psychosocial and/or psychiatric assessments may lead to the need for medications, psychotherapy, and/or support groups. Lastly, an assessment of overall health status may lead to approaches for minimizing visits to emergency rooms and hospitalizations.[29,30]

Conclusion

Patients with Gp symptoms are becoming increasingly recognized and referred to gastroenterologists. Better understandings of the pathophysiology of the spectrum of gastroparesis syndromes, assisted by innovations in diagnosis, have led to expansion of existing and new therapeutic approaches. Fortunately, most patients can benefit from a standardized diagnostic approach and directed noninvasive therapies. Patients with refractory gastroparesis symptoms, often with complex issues referred to gastroenterologists, remain a challenge, and novel approaches may improve their quality of life. ■

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

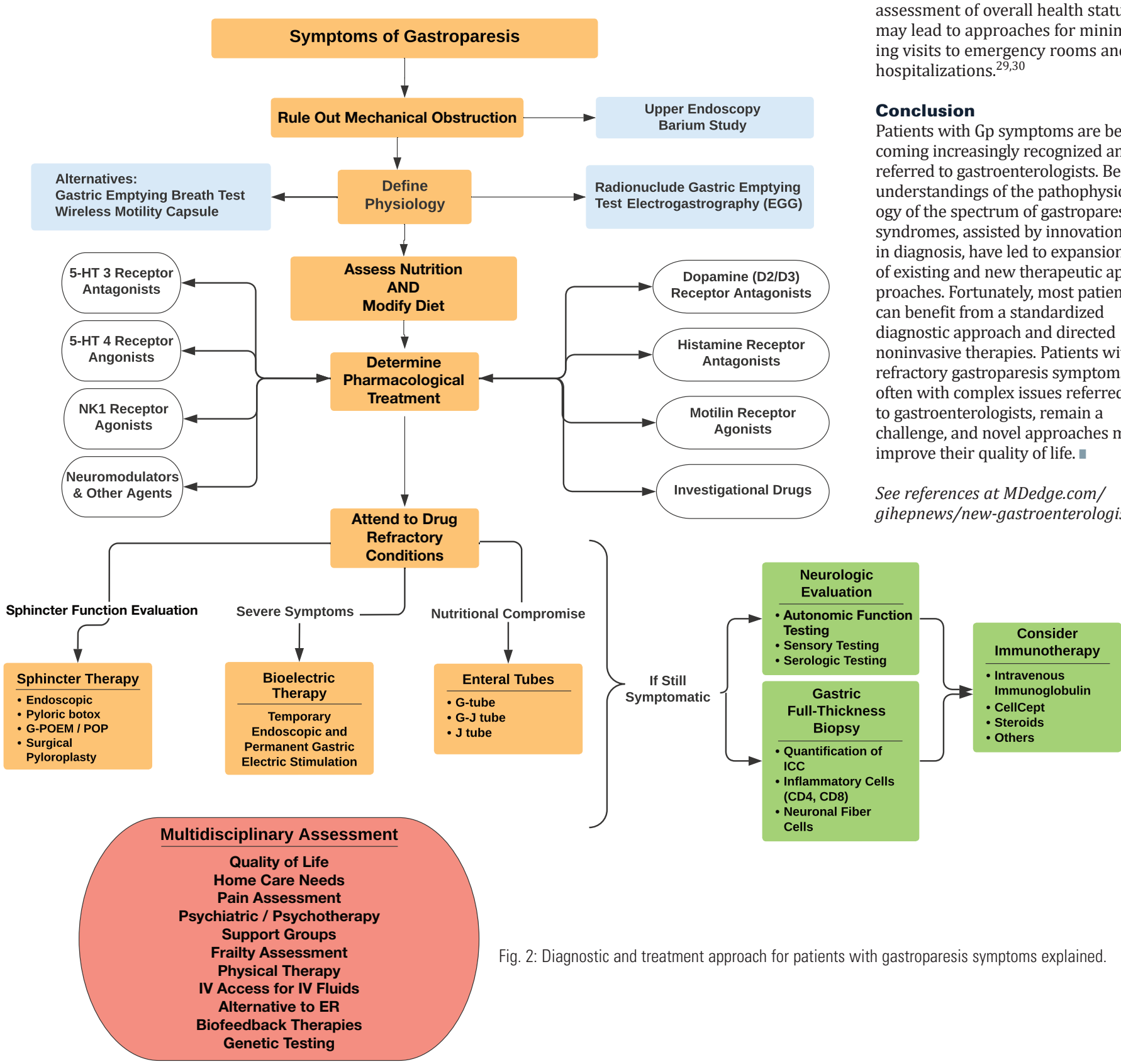

Fig. 2: Diagnostic and treatment approach for patients with gastroparesis symptoms explained.

Dr. Prateek Mathur and Dr. Thomas L. Abell

Moving the field forward

Index *from page 1*

activity, but they haven't been widely used because of their complexity, the authors wrote. They believe this index can be applied easily and efficiently in clinical practice. "Since a pathologist needs only to identify neutrophils, which is a part of routine in reading biopsy slides as clinical histopathological evaluation, one can have the PHRI score immediately without making additional effort and spending extra time.

Dr. Gui

Thus, the PHRI score can also be easily included into the pathology reports."

The researchers found that the index correlates strongly with endoscopic activity and predicts UC clinical outcomes, including hospitalization, colectomy, and initiation or changes in treatment caused by UC flare-up.

Dr. Gui's team developed the index using 614 biopsies from 307 patients with UC from 11 centers in Europe and North America who were prospectively enrolled in the PICaSSO study.

The index was a collaboration between pathologists and endoscopists who wanted a histologic score that would align with the endoscopic score and go beyond endoscopic evaluation. Specifically it eliminates consideration of ulceration/erosion, which is often a factor considered in other indices, because variability can be high without contributing much to accuracy.

Keen interest in histologic remission

David T. Rubin, MD, AGAF, chief of gastroenterology, hepatology, and nutrition and the codirector of the Digestive Diseases Center at the University of Chicago, noted continued interest in whether histologic findings (biopsies) of the mucosa are a clinically important and reachable treatment goal with UC.

"It's important to acknowledge that it is not yet a target of treatment, in part because of a variety of challenges and unknowns related to it," he said.

The current study addresses a major barrier to incorporation of histology in the clinical management of patients with UC, namely individual interpretation. "Development of this simplified novel scoring approach with artificial intelligence could be a major step forward. We are hopeful that this type of AI approach will eliminate some of the barriers to use of histology as a marker of treatment control. It is of interest to note that this novel score correlated to the endoscopic appearance, but didn't necessarily demonstrate superiority to it. This is important, since we have hypothesized that histology may provide more information about outcomes than endoscopy alone," Dr. Rubin said.

Dr. Rubin

He added that PHRI will need broader validation and incorporation into meaningful interventions before it can be incorporated into clinical practice, but he did note that, despite that, "this type of technological innovation is what the field needs in order to move forward."

The authors and Dr. Rubin declared no relevant financial conflicts. Two coauthors are funded by the NIHR Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham (England). ■

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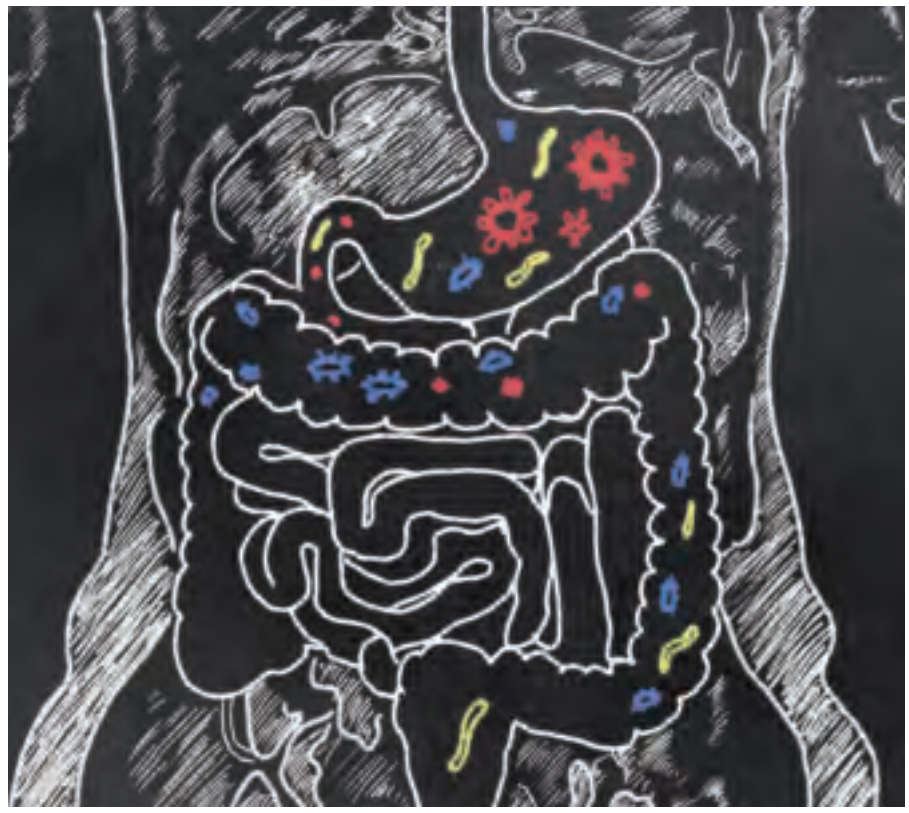
The future of microbiome therapies in *C. diff*, cancer

BY CHRISTINE KILGORE
MDedge News

FROM GMFH 2022



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Research on standardized microbiome-based therapies designed to prevent the recurrence of *Clostridioides difficile* infection (CDI) is moving "with a lot of momentum," according to one expert, and modulation of the gut microbiome may even enhance responses to immunotherapy and/or abrogate toxicity, according to another.

Several products for prevention of CDI recurrence are poised for either phase 3 trials or upcoming Food and Drug Administration approval, Sahil Khanna, MBBS, MS, AGAF, professor of medicine, gastroenterology, and hepatology at the Mayo Clinic in Rochester, Minn., reported at the 2022 Gut Microbiota for Health World Summit, organized by the American Gastroenterological Association and the European Society of Neurogastroenterology and Motility.

Jennifer A. Wargo, MD, MMSc, of the University of Texas MD Anderson Cancer Center, Houston, described her investigations of microbiome modulation's role in cancer treatment. "I used to say yes [we can do this] somewhat enthusiastically without data, but now we have data to support this," she said at the meeting. "The answer now is totally yes."

New approaches for CDI

"Based on how the field is moving, we might be able to [offer our patients] earlier microbiome restoration" than is currently afforded with fecal microbiota transplantation (FMT), Dr. Khanna said. "Right now the [Food and Drug Administration] and our clinical guidelines say we should do FMT after three or more episodes [of CDI] – that's heartbreaking for patients."

Several of the microbiome-based therapies under investigation – including two that have completed phase 3 trials – have shown efficacy after a second episode of CDI, and one of these two has also had positive results after one episode of CDI in patients 65 at older, a group at particularly high risk of recurrence, said Dr. Khanna.

The value of standardized, mostly pill-form microbiome therapies has been heightened during the pandemic. "We've been doing conventional FMT for recurrent *C. difficile* for over a decade now, and it's probably the most effective treatment we have," said Colleen R. Kelly, MD, AGAF, associate professor of medicine at Brown University, Providence, R.I., and moderator of the session on microbiota-based therapies.

Prepandemic "it got really hard, with issues of identifying donors, and quality control and safety ... And then when COVID hit the stool banks shut down," she said in an interview after the meeting. With stool testing for SARS-CoV-2 now in place, some stool is again available, "but it made me realize how fragile our current system is," Dr. Kelly said. "The fact that companies are putting these products through the FDA pipeline and investigating them in rigorous, scientific randomized controlled trials is really good for the field."

The products vary in composition; some are live multi-strain biotherapeutics derived from donor stool, for instance, while others are defined live bacterial consortia not from stool. Most are oral formulations, given one or multiple times, that do not require any bowel preparation.

One of the products most advanced in the pipeline, RBX2660 (Rebiotix, Ferring Pharmaceuticals) is stool derived and rectally administered. In phase 3 research, 70.5% of patients who received one active enema after having had two or more CDI recurrences and standard-of-care antibiotic treatment had no additional recurrence at 8 weeks compared to 58.1% in the placebo group, Dr. Khanna said.

> **"Based on how the field is moving, we might be able to [offer our patients] earlier microbiome restoration" than is currently afforded with FMT.**

The other product with positive phase 3 results, SER-109 (Seres Therapeutics), is a donor stool–derived oral formulation of purified *Firmicutes* spores that is administered after bowel prep. In results published earlier this year, the percentage of patients with recurrence of CDI up to 8 weeks after standard antibiotic treatment was 12% in the SER-109 group and 40% in the placebo group (N Engl J Med. 2022 Jan 20;386[3]:220-9).

Patients in this trial were required to have had three episodes of CDI, and interestingly, Dr. Khanna said, the diagnosis of CDI was made only by toxin enzyme immunoassay (EIA). Earlier phase 2 research, which allowed either toxin EIA or polymerase chain reaction testing for the diagnosis of CDI (as other trials have done), produced negative results, leading investigators to surmise that some of the included patients had been colonized with *C. difficile* rather than being actively infected, Dr. Khanna said.

Researchers of these trials are documenting not only resolution of CDI but what they believe are positive shifts in the gut microbiota after microbiome-based therapy, he said. For instance, a phase 1 trial he led of the product RBX7455 (Rebiotix, Ferring Pharmaceuticals) – an oral capsule of lyophilized stool–based bacteria that can be kept for several days at room temperature – showed increases in *Bacteroides* and *Clostridia*.

And other trials' analyses of microbiome engraftment have demonstrated that "you can restore [species] even when these bacteria aren't [included in the therapy]," he noted. "As the milieu of the gut improves, species that were not detected start coming back up."

Asked about rates of efficacy in the trials' placebo arms, Dr. Khanna said that "we've become smarter with our antibiotic regimens. ... The placebo response rate is the response to newer guideline-based therapies."

In addition to CDI, microbiome–based therapies are being studied, mostly in phase 1 research, for indications such as Crohn's disease, ulcerative colitis, autism spectrum disorder, hepatitis B, and hepatic encephalopathy, Dr. Khanna noted.

Dr. Kelly, whose own research has focused on FMT for CDI, said she anticipates an expansion of research into other indications once products to prevent CDI recurrence are on the market. "There have been a couple of promising ulcerative colitis trials that haven't gone anywhere clinically yet," she said in the interview. "But will we now identify patients with [ulcerative colitis] who may be more sensitive to microbial manipulation, for whom we can use these microbial therapies along with a biologic?"

Some of her patients with IBD

AGA resource

Help your patients understand their *C. difficile* diagnosis by sending them the following resource from the AGA GI Patient Center: https://patient.gastro.org/clostridioides-difficile-c-diff/.

and CDI who are treated with FMT have not only had their CDI eradicated but have subsequently seen improvements in their IBD, she noted.

The role of traditional FMT and of stool banks will likely change in the future with new standardized oral microbiome-based therapies that can be approved and regulated by the FDA, Dr. Kelly said. However, "we think the stool banks will still have some value," she said, certainly for clinical research and probably for some treatment purposes as well. Regarding new therapies, "I just really hope they're affordable," she said.

Gut microbiome manipulation for cancer

Dr. Wargo's research at MD Anderson has focused on metastatic breast cancer and immunotherapeutic checkpoint blockade. By sequencing microbiota samples and performing immune profiling in hundreds of patients, her team found that responders to PD-1 blockage have a greater diversity of gut bacteria and that "favorable signatures in the gut microbiome" are associated with enhanced immune responses in the tumor microenvironment.

Studies published last year in Science from investigators in Israel (2021 Feb 5;371[6529]:602-9) and Pittsburgh (2021 Feb 5;371[6529]:595-602), demonstrated that FMT promotes response in immunotherapy-refractory melanoma patients. In one study, FMT provided clinical benefit in 6 of 15 patients whose cancer had progressed on prior anti-PD-1 therapy, "which is pretty remarkable," Dr. Wargo said.

Both research groups, she noted, saw favorable changes in the gut microbiome and immune cell infiltrates both at the level of the colon and the tumor.

Current research on FMT and other microbiome-modulation strategies for cancer is guided in part by knowledge that tumors have microbial signatures – these signatures are now being identified across all tumor types – and by findings of "crosstalk" between the gut and tumor microbiomes, she explained.

"Researchers are working hard to identify optimal consortia to enhance immune responses in the cancer setting, with promising work in preclinical models," she said, and clinical trials are in progress. The role of diet in modulating the microbiome and enhancing anti-tumor immunity, with a focus on high dietary fiber intake, is also being investigated, she said.

Dr. Wargo reported that she serves on the advisory boards and is a paid speaker of numerous pharmaceutical and biotechnology companies, and is the coinventor of a patent submitted by the Texas MD Anderson Cancer Center on modulating the microbiome to enhance response to checkpoint blockade, and another related patent. Dr. Khanna reported that he is involved in research with Ferring/Rebiotix, Finch, Seres, Pfizer and Vedanta, and does consulting for Immuron and several other companies. Dr. Kelly said she serves as an unpaid adviser for OpenBiome, a nonprofit stool bank, and that her site has enrolled patients in two of the trials testing products for CDI.

The 2022 Gut Microbiota for Health World Summit was supported by sponsorships from Danone, Ferring Pharmaceuticals, Aimmune Therapeutics and Seres Therapeutics, Sanofi, and Intrinsic Medicine with additional support from educational grants provided by Ferring Pharmaceuticals and Salix Pharmaceuticals. ■

AGA resource

Get the latest information on the gut microbiome on the AGA website: https://gastro.org/research-and-awards/gut-microbiome/.

Malnutrition common in patients with IBD

BY NEIL OSTERWEIL
MDedge News

Malnutrition is common among patients with inflammatory bowel disease (IBD) and is associated with worse outcomes that can prolong hospitalizations and increase patients' risk for death.

As many as 85% of inpatients with IBD may be malnourished, with the severity of malnutrition affected by disease activity, extent, and duration, said Kelly Issokson, MS, RD, CNSC, clinical nutrition coordinator in the IBD program in the division of gastroenterology at Cedars-Sinai Medical Center, Los Angeles.

"Malnutrition is a severe complication of IBD, and it should not be overlooked," she said during an oral presentation at the annual Crohn's & Colitis Congress®, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association.

In patients with IBD, malabsorption, enteric losses, inadequate intake, and side effects of medical therapy can all lead to malnutrition, which in turn is an independent risk factor for venous thromboembolic events, nonelective surgery, longer hospital stays, and increased mortality.

In addition, malnutrition in IBD increases risk for infection and sepsis, and for perioperative complications, and can more than double the cost of care, compared with adequately nourished IBD patients, she said.

Ms. Issokson cited a definition of malnutrition from the American Society of Parenteral and Enteral Nutrition as "an acute or chronic state of overnutrition or undernutrition with or without inflammatory activity that has led to a change in body composition and diminished function."

Lab findings of low albumin, low prealbumin, or isolated metrics such as weight loss or change in body mass index do not constitute malnutrition and should not be used to diagnosis it, Ms. Issokson cautioned.

Patients at low risk for malnutrition have no unintentional weight loss, are eating well, have minimal or no dietary restrictions, and no wasting. In contrast, high-risk patients have unintentional weight loss, have decreased appetite and/or food intake, restrict multiple foods, or show signs of wasting.

NES/E+/GETTY IMAGES

Screening

"Nutrition screening is the first step in diagnosing a patient with malnutrition. This is a process of identifying individuals who may be at nutrition risk and benefit from assessment from a registered dietitian," Ms. Issokson said.

The Malnutrition Screening Tool is quick, easy to administer, and requires minimal training. It can be used to screen adults for malnutrition regardless of age, medical history, or setting, she said.

The two-item instrument asks, "Have you recently lost weight without trying?" with a "no" scored as 0 and a "yes" scored as 2. The second question is, "Have you been eating poorly because of decreased appetite, with a "no" equal to 0 and a "yes" equal to 1. Patients with a score of 0 or 1 are not at risk, whereas patients with scores of 2 or 3 are deemed to be at risk for malnutrition and require further assessment by a dietitian.

Ms. Issokson

Assessment

Assessment for malnutrition involves a variety of factors, including anthropometric factors such as weight and body mass index changes; biochemical markers such as fat-soluble vitamins, water-soluble vitamins, minerals, and urinary sodium; symptoms such as decreased appetite, abdominal pain, cramping or bloating, diarrhea, or urgency or obstructive symptoms; and body composition measures such as handgrip strength, biochemical impedance analysis, skinfold thickness, bone mineral density, and muscle mass.

Other nutritional assessment tools may include 24-hour recall of nutrition intake, diet history, and questions about eating behaviors, food allergies or intolerances, and cultural or religious food preferences.

Assessing food security is also important, especially during the current pandemic, Ms. Issokson emphasized.

"Is your patient running out of food? Do they have money to purchase food? Are they able to go to the grocery store to buy food? This is essential to know when you're developing a nutrition plan," she said.

A nutrition-focused physical exam should include assessment of skin manifestation, secondary to malnutrition or malabsorption, such as dry skin, delayed wound healing, stomatitis, scurvy, seborrheic dermatitis, bleeding, and periorificial and acral dermatitis or alopecia.

Diagnosis

Currently available malnutrition criteria have not been validated for use in patients with IBD, and further studies are needed to affirm their applicability to this population, Ms. Issokson said.

The Academy of Nutrition and Dietetics–American Society for Parenteral and Enteral Nutrition (AND-ASPEN) malnutrition criteria require measures of weight loss, energy intake, subcutaneous fat loss, subcutaneous muscle loss, general or local fluid accumulation, and handgrip strength to determine whether a patient is moderately or severely malnourished.

Ms. Issokson said that she finds the European Society for Clinical Nutrition and Metabolism Global Leadership Initiative on Malnutrition (ESPEN GLIM) criteria somewhat easier to use for diagnosis, as they consist of phenotypic and etiologic criteria, with patients who meet at least one of each being considered malnourished.

"When identified, document malnutrition, and of course intervene appropriately by referring to a dietitian providing education and supporting the patient to help them optimize their nutrition and improve their outcomes," she concluded.

In a discussion following the session, panelist Neha Shah, MPH, RD, CNSC, a dietitian and health education specialist at the University of California, San Francisco, commented on the importance of malnutrition assessment in patients with IBD being considered for surgery.

Patients should be screened for malnutrition, and if they have a positive screen, "should be automatically referred to a registered dietitian specializing in IBD for a nutrition assessment," she said.

"Certainly, a nutritional assessment, as Kelly has highlighted really well, will encompass an evaluation of various areas of health – patient history, food and nutrition history, changing anthropometrics, alterations in labs – and certainly going into further nutrition history with net food intolerance, intake from each food group, portions, access, support, culture, eating environment, skills in the kitchen, relationship with diet."

Ms. Issokson is a board member of the Crohn's & Colitis Foundation and a digital advisory board member of Avant Healthcare. Ms. Shah had no disclosures. ■

Less cirrhosis but worse outcomes for Black patients

BY LAIRD HARRISON

Compared with White people, Black people are less likely to develop cirrhosis from nonalcoholic steatohepatitis (NASH) but are more likely to die when hospitalized with this condition, researchers say.

The finding highlights the importance of addressing hepatic complications and nonhepatic comorbidities with a comprehensive and interdisciplinary approach that includes social determinants of health, said Emad Qayed, MD, MPH, AGAF, an associate professor of medicine at Emory University School of Medicine, Atlanta.

The study by Dr. Qayed and colleagues was published in the Journal of Clinical Gastroenterology (2022 Apr 1. doi: 10.1097/MCG.0000000000001698).

Previous studies have indicated that Black people are less likely than White people to develop nonalcoholic fatty liver disease (NAFLD), despite the fact that prevalence is increasing. Furthermore, when Black people do develop NAFLD, the disease is less likely to progress to NASH. In cases in which NASH does develop, the evidence has been mixed as to the effect of race on hospital outcomes.

To shed new light on that question, Dr. Qayed and colleagues analyzed data from 2016 to 2018 from the National Inpatient Sample, which is produced by the Healthcare Cost and Utilization Project and is sponsored by the Agency of Healthcare Research and Quality.

They identified 43,409 hospitalizations for NASH, with 41,143 White patients and 2,266 Black patients. The mean age of the Black patients was less than that of the White patients (56.4 years vs. 63.0 years), and Black patients were more likely to be women (69.9% vs. 61.6%).

More of the Black patients had hypertension, obesity, chronic kidney disease, and congestive heart failure, while more of the White patients had diabetes, dyslipidemia, and ischemic heart disease.

Among the Black patients, 33.6% had cirrhosis, compared with 56.4% of the White patients. Likewise, among the Black patients, there were fewer manifestations of decompensated cirrhosis, compared with the White patients. Black patients were also less likely to have had to undergo upper endoscopy and paracentesis.

The Black patients died in the hospital at a rate of 3.9%, which was not significantly higher than the 3.7% rate for the White patients (unadjusted odds ratio, 1.06; 95% confidence interval, 0.84-1.32; $P = .6$). But, when the researchers adjusted for age, sex, cirrhosis, risk of mortality (based on the overall number and severity of diseases), and insurance status, there were significantly higher odds of mortality among the Black patients (adjusted OR, 1.34; 95% CI, 1.05-1.71; $P = .018$).

They did not find any association between hospital size, location, or region with mortality.

They also found no difference in mortality between Black patients and White patients among those those with and those without cirrhosis. However, they found that Black patients were more likely to have acute kidney injury, chronic kidney disease, and congestive heart failure.

Regarding the reasons for hospitalization, the researchers found liver-related illnesses, such as hepatic failure and noninfectious hepatitis, to be most common among the White patients. Circulatory disorders, such as heart failure, and endocrine disorders, such as diabetes mellitus with complications, were found to be most common among the Black patients.

The length of time in the hospital was longer for the Black patients than the White patients (6.3 days vs. 5.6 days; $P < .0001$). The cost of hospitalization was higher for Black patients as well ($18,603 vs. $17,467). This suggests that Black patients were sicker overall, despite their lower rates of liver complications.

"Clinicians should consider NASH as part of the metabolic syndrome," Paul Martin, MD, AGAF, chief of digestive health and liver diseases at the University of Miami, told this news organization. He was not involved in the study.

"Typically, these patients have a number of risk factors for fatty liver, including obesity and often hyperlipidemia, hypertension, and sleep apnea," he said. "Clinicians should screen their patients for such comorbidities and then treat them."

Dr. Qayed and Dr. Martin reported no relevant financial relationships. ■

CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

BY JOON WOO PARK, DONG HOON BAEK, AND SO JEONG LEE

Previously published in Gastroenterology (2020 Feb;158[3]:482-4).

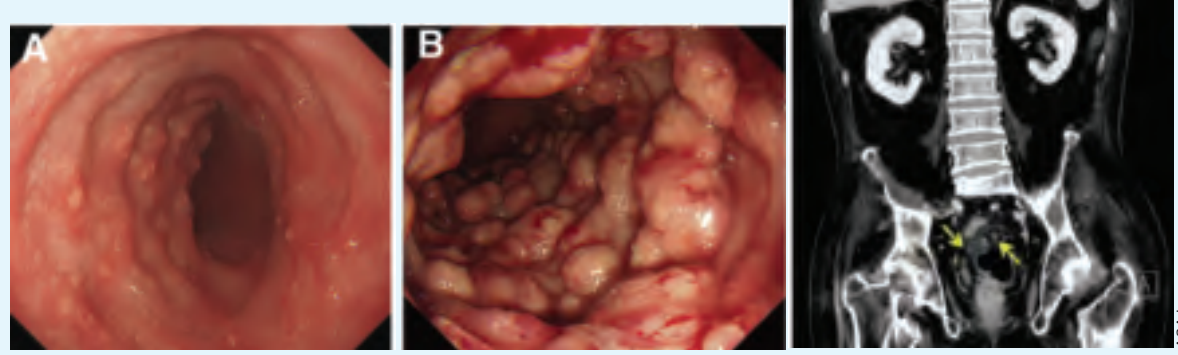
A 60-year-old man with C3 tetraplegia was referred to our department for evaluation of abdominal pain and hematochezia. He was diagnosed with adrenal insufficiency 5 years prior and has been taking low-dose prednisolone (7.5 mg) once a day. One year before presentation, he complained of intermittent loose, mucoid stool and abdominal pain. Sigmoidoscopy revealed multiple small yellowish plaques in the sigmoid colon (Figure A). However, symptoms improved without any treatment, and he was discharged from the rehabilitation department. He was readmitted for respiratory rehabilitation owing to dyspnea. On hospital day 4, he complained of abdominal pain and passing loose stool with foul odor 4-5 times a day. On hospital day 7, the abdominal pain worsened, and hematochezia occurred.

On physical examination, he was hemodynamically stable and afebrile. The abdomen was soft with mild tenderness on palpation in the periumbilical area without peritoneal signs. Laboratory studies were notable with a hemoglobin level of 10.7 g/dL, total protein of 4.09 g/dL, and albumin of 2.21 g/dL. Inflammatory marker (C-reactive protein) was mildly elevated to 1.83 mg/dL. Serology for human immunodeficiency virus was negative. Tumor markers, such as carcinoembryonic antigen, carbohydrate antigenic determinant, and alpha-fetoprotein, were within the normal range. Antineutrophil cytoplasmic antibody was negative, and rheumatic factor was within the normal range. Findings from stool for acid-fast bacillus and *Clostridioides difficile* toxin were negative; no pathogens were cultured, and no parasites were identified.

Sigmoidoscopy revealed diverse, multiple polypoid lesions (3-10 mm) with erythema, edema, and friability surrounding the entire lumen on the sigmoid colon (Figure B). The number and size of the polypoid lesions increased compared with the endoscopic findings obtained 1 year prior. The lesions easily bled on contact. Multiple biopsies of different sites were taken. An abdominal computed tomography scan showed multiple polyps of <1 cm that were confined to the sigmoid colon (Figure C, arrow).

Based on this information, what is the most likely diagnosis?

The answer is on page 31.



Deprescribe only in certain situations

PPIs *from page 1*

to summarize the evidence and to provide the clinician with a single document which distills the evidence down into clinically applicable guidance statements," Laura Targownik, MD, associate professor of medicine at the University of Toronto and corresponding author of the practice update published in Gastroenterology (2022 Feb 16. doi: 10.1053/j.gastro.2021.12.247) said in an interview.

"PPIs are highly effective medications for specific gastrointestinal conditions, and are largely safe. However, PPIs are often used in situations where they have minimal and no proven benefit."

"PPIs are highly effective medications for specific gastrointestinal conditions, and are largely safe. However, PPIs are often used in situations where they have minimal and no proven benefit, leading to unnecessary health care spending and unnecessary exposure to drugs. Our paper helps clinicians identify which patients require long-term PPI use as well as those who may be using them unnecessarily, and provides actionable advice on how to deprescribe PPIs from those deemed to be using them without clear benefit," said Dr. Targownik.

An estimated 7%-15% of health care patients in general and 40% of those over 70 use PPIs at any given time, making them among the most commonly used drugs. About one in four patients who start PPIs will use them for a year or more. Aside from their use for acid-mediated upper gastrointestinal conditions, PPIs often find use for less well-defined complaints. Since PPIs are available over the counter, physicians may not even be involved in a patient's decision to use them.

Although PPI use has been associated with adverse events, including chronic kidney disease, fractures, dementia, and greater risk of COVID-19 infection, there is not high-quality evidence to suggest that PPIs are directly responsible for any of these adverse events.

Dr. Targownik

The authors suggested the primary care provider should periodically review and document the complaints or indications that prompt PPI use. When a patient is found to have no chronic condition that PPIs could reasonably address, the physician should consider a trial withdrawal. Patients who take PPIs twice daily for a known chronic condition should be considered for a reduction to a once-daily dose.

In general, PPI discontinuation is not a good option for most patients with complicated gastroesophageal reflux disease, such as those with a history of severe erosive esophagitis, esophageal ulcer, or peptic stricture. The same is true for patients with Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis.

Before any deprescribing is considered, the patient should be evaluated for risk of upper gastrointestinal bleeding, and those at high risk are not candidates for PPI deprescribing.

When the decision is made to withdraw PPIs, the patient should be advised of an increased risk of transient upper gastrointestinal symptoms caused by rebound acid hypersecretion.

The withdrawal of PPIs can be done abruptly, or the dose can be tapered gradually.

PPI-associated adverse events should not be a consideration when discussing the option of withdrawing from PPIs. Instead, the decision should be based on the absence of a specific reason for their use. A history of such adverse events, or a current adverse event, should not be a sole reason for discontinuation, nor should risk factors associated with risk of adverse events. Concerns about adverse events have driven recent interest in reducing use of PPIs, but those adverse events were identified through retrospective studies and may be only associated with PPI use rather than caused by it. In many cases there is no plausible mechanistic cause, and no clinical trials have demonstrated increased adverse events in PPI users.

Three-quarters of physicians say they have altered treatment plans for patients because of concerns about PPI adverse events, and 80% say they would advise patients to withdraw PPIs if they learned the patient was at increased risk of upper gastrointestinal bleeding. Unnecessary withdrawal can lead to recurrent symptoms and complications when PPIs are effective treatments. "Therefore, physicians should not use concern about unproven complications of PPI use as a justification for PPI deprescribing if there remain ongoing valid indications for PPI use," the authors wrote.

Dr. Targownik has received investigator-initiated funding from Janssen Canada and served on advisory boards for AbbVie Canada, Takeda Canada, Merck Canada, Pfizer Canada, Janssen Canada, Roche Canada, and Sandoz Canada. She is the lead on an IBD registry supported by AbbVie Canada, Takeda Canada, Merck Canada, Pfizer Canada, Amgen Canada, Roche Canada, and Sandoz Canada. None of the companies with whom Dr. Targownik has a relation are involved in the manufacturing, distribution, or sales of PPIs or any other agents mentioned in the manuscript. ■

AGA Clinical Practice Update: Expert Review

Personalizing GERD diagnosis and treatment

BY JIM KLING
MDedge News

A recent American Gastroenterological Association Clinical Practice Update for evaluation and management of gastroesophageal reflux disease (GERD) focuses on delivering personalized diagnostic and therapeutic strategies.

The document includes new advice on use of upfront objective testing for isolated extraesophageal symptoms, confirmation of GERD diagnosis prior to long-term GERD therapy even in PPI responders, as well as important elements focused on personalization of therapy.

Although GERD is common, with an estimated 30% of people in the United States experiencing symptoms, up to half of all individuals on proton-pump inhibitor (PPI) therapy report incomplete symptom improvement. That could be due to the heterogeneous nature of symptoms, which may include heartburn and regurgitation, chest pain, and cough or sore throat, among others. Other conditions may produce similar symptoms or could be exacerbated by the presence of GERD.

The authors of the expert review, published in Clinical Gastroenterology and Hepatology (2022 Feb 2. doi: 10.1016/j.cgh.2022.01.025), note that these considerations have driven increased interest in personalized approaches to the management of GERD. The practice update includes sections on how to approach GERD symptoms in the clinic, personalized diagnosis related to GERD symptoms, and precision management.

In the initial management, the authors offer advice on involving the patient in creating a care plan, the patient educating, and conducting a 4- to 8-week PPI trial in patients with heartburn, regurgitation, or noncardiac chest pains without accompanying alarm signals. If symptoms don't improve to the patient's satisfaction, dosing can be boosted to twice per day, or a more effective acid suppressor can be substituted and continued at a once-daily dose. When the response to PPIs is adequate, the dose should be reduced until the lowest effective dose is reached, or the patient could potentially be moved to H_2-receptor antagonists (H2RA) or other antacids. However, patients with erosive esophagitis, biopsy-confirmed Barrett's esophagus, or peptic stricture must stay on long-term PPI therapy.

The authors also gave advice on when to conduct objective testing. When a PPI trial doesn't adequately address troublesome heartburn, regurgitation, and/or noncardiac chest pain, or if alarm systems are present, endoscopy should be employed to look for erosive reflux disease or

Continued on following page

THARAKORN/GETTY IMAGES

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long-segment Barrett's esophagus as conclusive evidence for GERD. If these are absent, prolonged wireless pH monitoring while a patient is off medication is suggested. In addition, patients with extraesophageal symptoms suspected to be caused by reflux should undergo upfront objective reflux testing while off PPI therapy rather than doing an empiric PPI trial.

With an estimated 30% of people in the United States experiencing symptoms, up to half of all individuals on proton-pump inhibitor therapy report incomplete symptom improvement.

The authors advise that, if patients don't have proven GERD and are continued on PPI therapy, they should be evaluated within 12 months to ensure that the therapy and dose are appropriate. Physicians should offer endoscopy with prolonged wireless reflux monitoring in the absence of PPI therapy (ideally after 2-4 weeks of withdrawal) to confirm that long-term PPI therapy is needed.

In the section on personalization of disease management, the authors note that ambulatory reflux monitoring and upper gastrointestinal endoscopy can be used to guide management of GERD. When upper GI endoscopy reveals no erosive findings and esophageal acid exposure time (AET) is less than 4% throughout all days of prolonged wireless pH monitoring, the physician can conclude that the patient has no pathologic gastroesophageal reflux and is likely to have a functional esophageal disorder. In contrast, erosive findings during upper GI endoscopy and/or AET more than 4% across at least 1 day of wireless pH monitoring suggests a GERD diagnosis.

Optimization of PPI is important among patients with GERD, and the authors stress that patients should be educated about the safety of PPI use.

Adjunctive pharmacotherapy is useful and can include alginate antacids for breakthrough symptoms, H2RAs for nocturnal symptoms, baclofen to counter regurgitation or belching, and prokinetics for accompanying gastroparesis. The choice of medications depends on the phenotype, and they should not be used empirically.

For patients with functional heartburn or reflux disease linked to esophageal hypervigilance, reflux sensitivity, or behavioral disorders, options include pharmacologic neuromodulation, hypnotherapy provided by a behavioral therapist, cognitive-behavioral therapy, and diaphragmatic breathing and relaxation.

If symptoms persist despite efforts at optimization of treatments and lifestyle factors, ambulatory 24-hour pH-impedance monitoring on PPI can be used to investigate mechanistic causes, especially when there is no known antireflux barrier abnormality, but the technique requires expertise to correctly interpret. This can ensure that the symptoms are not due to reflux hypersensitivity, rumination syndrome, or a belching disorder. When symptoms are confirmed to be treatment resistant, therapy should be escalated, using a strategy that incorporates a pattern of reflux, integrity of the antireflux barrier, obesity if present, and psychological factors.

Surgical options for confirmed GERD include laparoscopic fundoplication and magnetic sphincter augmentation. Transoral incisionless fundoplication can be performed endoscopically in selected patients. For obese patients with confirmed GERD, Roux-en-Y gastric bypass is effective at reducing reflux and can be used as a salvage treatment for nonobese patients. Sleeve gastrectomy may exacerbate GERD.

The authors reported relationships with Medtronic, Diversatek, Ironwood, and Takeda. The authors also reported funding from National Institutes of Health grants. ■

Vibrating wearable device may help nighttime GERD

BY MARCIA FRELLICK

A vibrating wearable device helped people with gastroesophageal reflux disease (GERD) stay positioned on their left side while sleeping, alleviating nighttime reflux symptoms compared with sham treatment, a small, randomized study suggests.

People often report having more reflux symptoms when sleeping on their right side, and experimental studies suggest that sleeping on the right side is associated with higher esophageal acid exposure time and slower esophageal acid clearance compared with sleeping on the left side, the authors wrote.

They cite a possible cause as the stomach being above the esophagus when a person is sleeping on their right side, resulting in more reflux.

"There are two very exciting new things that can be learned," Arjan Bredenoord, MD, PhD, a principal investigator of the study and professor of neurogastroenterology and motility at the Academic Medical Center in Amsterdam, said in an interview. "First, we show that a device that trains people to sleep on the left side really helps to relieve nocturnal reflux symptoms. Second, the study was performed completely remotely, with the patients being at home.

"The devices were shipped to the patients. All contact was via video calling, and questionnaires were done via links in emails that were linked to secure databases to store the patients' symptom responses," he added.

"First, we show that a device that trains people to sleep on the left side really helps to relieve nocturnal reflux symptoms. Second, the study was performed completely remotely, with the patients being at home."

The findings were published online in Clinical Gastroenterology and Hepatology (2022 Mar 13. doi: 10.1016/j.cgh.2022.02.058).

A study in sleep positional therapy

Researchers performed a double-blind, randomized, sham-controlled trial in 100 patients with nighttime GERD symptoms who wore a programmed device (about 1.5 inches square) on their chest, midsternum.

Patients were advised to sleep on their left side and randomly assigned (1:1) either to a group whose device produced a gentle vibration when they flipped onto their right side throughout sleep or to the group whose device vibrated when they flipped to the right side but only for the first 20 minutes of use (the sham intervention).

The primary outcome for success in this study was defined as at least a 50% reduction in the Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire (N-GSSIQ) score. Secondary outcomes included change in sleep position and reflux symptoms.

In the intention-to-treat analysis, the rate of treatment success was 44% in the intervention group vs. 24% in the sham group. The risk difference was 20% (95% confidence interval, 1.8%-38.2%; $P = .03$).

Treatment led to a significant avoidance of sleeping on the right side (intervention 2.2% vs. sham 23.5%; $P \leq .0001$) and an increased time of sleeping on the left side (intervention 60.9% vs. sham 38.5%; $P \leq .0001$).

Patients in the intervention group also had more reflux-free nights (9 nights vs. 6 nights for the sham group).

After 2 weeks of treatment, the average total N-GSSIQ scores were lower in the active device group (18.8 vs. 23.7 in the sham group; $P = .04$).

Most with GERD have nighttime symptoms

The authors pointed out that up to 80% of patients with GERD experience symptoms during the night, such as heartburn and regurgitation, which can significantly impair sleep quality and daytime functioning.

Solutions are of high interest because current measures have shortcomings.

Raising the head-end of the bed and lengthening the time between dinner and bedtime have limited effect, the authors explained. And while proton pump inhibitors are very effective for daytime symptoms, they have limited efficacy for nighttime reflux symptoms.

Antireflux pillows, which are designed to keep patients on their left side through the night, have been found to result in less recumbent acid exposure and less self-reported nighttime reflux symptoms, but they do not allow for spontaneous body movements and can be uncomfortable, they explained.

The lightweight vibration device, made by Side Sleep Technologies BV, registers the sleep position of a subject at 30-second intervals. It categorizes sleep position as supine, right, left, prone, or upright.

Michiel Allessie, CEO of Side Sleep Technologies, said in an interview that the wearable V1.0 is sold as a consumer electronic device rather than a medical device in the United Kingdom. He said the company expects to sell the V1.0 in the United States starting in June, with a target price of $99.

Promising but device still needs real-world testing

When asked to comment, Philip Katz, MD, AGAF, a gastroenterologist at Weill Cornell Medicine in New York, said it was a fantastic study scientifically and academically incredibly interesting, but the device is not a panacea.

Dr. Katz said he will remain skeptical until the device is tested in real life, and added that it's important to remember this is one study with 100 people.

He also wondered whether there might be an even better solution in a well-designed wedge, for example, and whether the buzzing of this product might

Continued on following page

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affect sleep quality. If so, would that be worth the tradeoff?

Dr. Katz noted that busy physicians may not have the time to determine whether patients truly have nocturnal GERD or just similar symptoms. This study included people who were carefully screened by the researchers for nocturnal reflux symptoms, he pointed out.

Based on this study, Dr. Katz said he would tell patients, "You have a 50% chance to be helped because their primary outcome was met by 44%."

He said the decision is up to the patients and comes down to this: "It's better than nothing for sure. Is it worth $100? You tell me."

Dr. Bredenoord said the next step is a study using pH-impedance monitoring of the esophagus to show that there is also an effect on reflux episodes.

The investigational medical devices were provided free of charge and without restrictions by Side Sleep Technologies BV. Dr. Bredenoord disclosed research funding from Nutricia, Norgine, SST, Thelial, and Bayer; speaker and/or consulting fees from Laborie, Eso-Cap, Medtronic, Dr. Falk Pharma, Calypso Biotech, Alimentiv, Reckett Benkiser, Regeneron, and AstraZeneca; and previously owned shares in Side Sleep Technologies BV. Another coauthor received research funding from Boston Scientific and speaker and/or consulting fees from Cook and Olympus. The remaining authors have disclosed no relevant financial relationships. Dr. Katz reported being a consultant for Phathom Pharmaceuticals and Sebela.

AsiaVision/E+/Getty Images

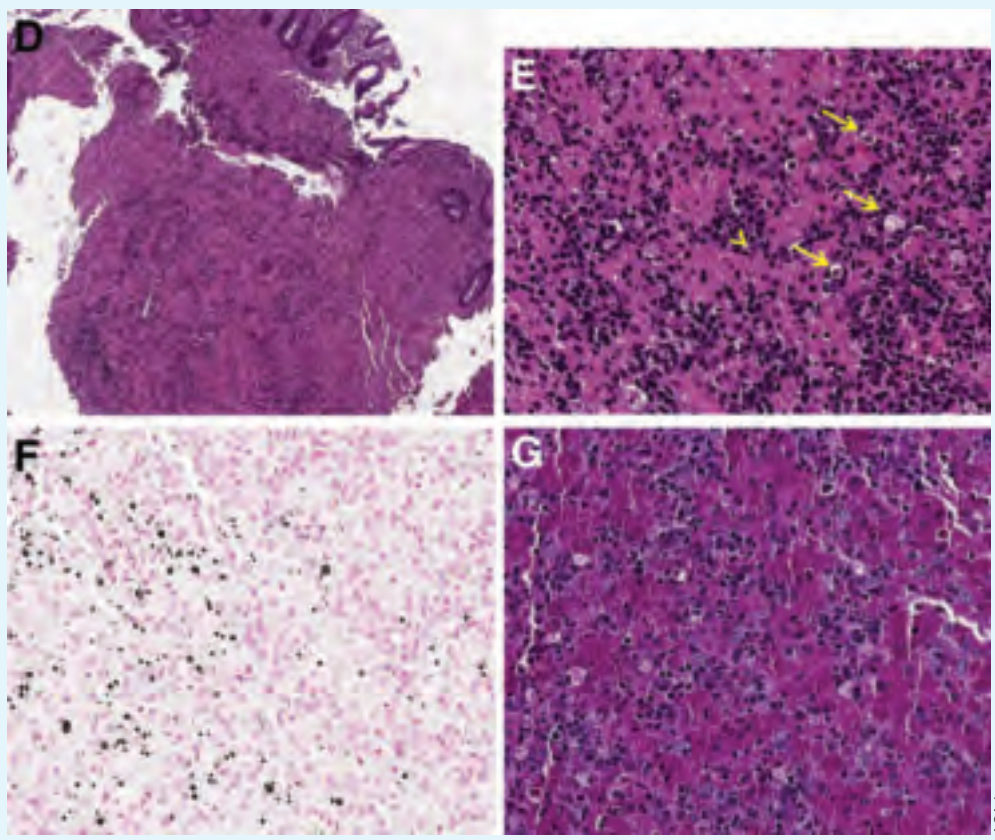
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" on page 27: Colonic malakoplakia

Histopathologic examination of the biopsy specimens revealed nodular mixed inflammatory cells and infiltration of the epithelioid histiocytes in lamina propria (Figure D; stain: hematoxylin and eosin; original magnification 40×). The histiocytes showed foamy and eosinophilic cytoplasm (Figure E, arrows) and some of them had a targetoid appearance (Figure E, arrowhead; stain: hematoxylin and eosin; original magnification 200×). Von Kossa stains highlighted the targetoid structures in the histiocytes (Figure F, Michaelis-Gutmann bodies). The granular cytoplasm of the histiocytes was positive on periodic acid-Schiff stain (Figure G). Based on these findings, the patient was diagnosed with colonic malakoplakia.

Malakoplakia is an uncommon, chronic, granulomatous inflammatory disease. It most commonly affects the urinary tract and gastrointestinal tract, but may occur at any anatomic site. Malakoplakia of the gastrointestinal tract are seen most frequently in the rectum and sigmoid and right colon.[1] It is diagnosed by the characteristic histologic feature of accumulated histiocytes with abundant eosinophilic granular cytoplasm containing basophilic inclusions, consistent with Michaelis-Gutmann bodies. Although the exact etiology and pathogenesis of malakoplakia are unclear, it seems to originate from an acquired defect in the intracellular destruction of phagocytosed bacteria, usually associated with *Escherichia coli*, *Klebsiella*, and *Mycobacterium*.[2] It can have various causes, such as immunosuppression, malignant neoplasms, systemic diseases, and genetic diseases. Clinical manifestation of colonic malakoplakia is diverse, ranging from asymptomatic to malaise, fever, abdominal pain, diarrhea, hematochezia, and intestinal obstruction. Granulomatous reaction of malakoplakia generates the endoscopic appearance of lesions, which ranges from plaques to nodules and yellow-brown masses. In the early stage, malakoplakia commonly presents as soft yellow to tan mucosal plaques endoscopically, as seen in our case (Figure A). As the disease progresses in the later stage, malakoplakia presents as raised, grey to tan polypoid lesions of various sizes with peripheral hyperemia and a central depressed area, as seen in our case (Figure B).[3] Because of this endoscopic morphology, colonic malakoplakia may be misdiagnosed as atypical lymphoma, familial adenomatous polyposis, and metastatic carcinoma. To date, the natural course of malakoplakia of the colon is unclear, and no guidelines for treatment, treatment methods, duration of treatment, or surveillance are currently available. However, treatment of malakoplakia is essential to reduce immunosuppression and includes antibiotics with intracellular action and choline agonists that replenish the decreased cyclic 3', 5'-guanosine monophosphate levels. In summary, although malakoplakia of the colon is very rare, it should be considered in the differential diagnosis of polypoid colonic lesions, especially in immunocompromised or malnourished patients.



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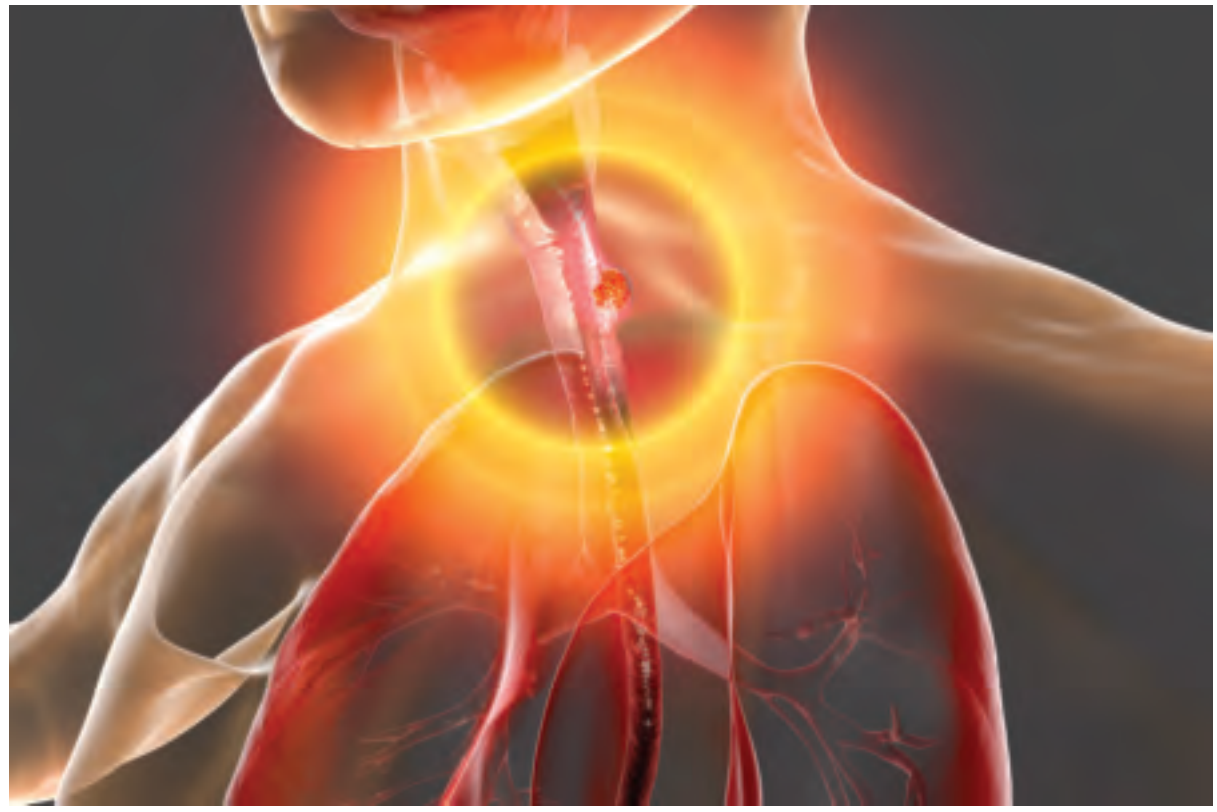
Radiofrequency ablation has long-lasting protective effects in esophageal cancer

BY MARCIA FRELLICK
Mdedge News


DR_MICROBE/ISTOCK/GETTY IMAGES

Radiofrequency ablation (RFA) is effective and long lasting in preventing esophageal adenocarcinoma, new data suggest.

Researchers, led by Paul Wolfson, MBBS, from the Wellcome/EPSRC (Engineering and Physical Sciences Research Council) Centre for Interventional & Surgical Sciences, University College London, also found that most treatment relapses happen early and can be re-treated successfully.

Findings were published in a final 10-year report from the United Kingdom National Halo Radiofrequency Ablation Registry and in Gastrointestinal Endoscopy (2022 Feb. doi: 10.1016/j.gie.2022.02.016). Because RFA has been used in mainstream clinical practice only since 2005, long-term data of more than 5 years hasve been lacking.


Dr. Kumar

Multiple studies have shown that RFA is effective in preventing esophageal cancer, but data have been lacking on how long RFA is effective in preventing esophageal adenocarcinoma in patients with dysplastic Barrett's esophagus (BE).

A significant number of patients with dysplastic BE do not initially have visible lesions. For instance, the U.S. RFA Patient Registry reported an average 2.7-year follow-up of 4,982 patients, but only 1,305 had dysplasia, the authors of the U.K. report note.

"It is well-established that endoscopic treatment of dysplastic BE is initially successful in up to 90% of patients," the authors wrote. "What is less well understood is how long that benefit lasts and if this contributes to a substantial reduction in progression to cancer."

Researchers prospectively gathered data from 2,535 patients from 28 U.K. specialist centers who underwent RFA therapy for BE (average length 5.2 cm, range 1-20 cm). Among the group, 20% had low-grade dysplasia, 54% had high-grade dysplasia, and 26% had intramucosal carcinoma.

They looked at rates of invasive cancer and analyzed data for 1,175 patients to assess clearance rates of dysplasia (CR-D) and intestinal metaplasia (CR-IM) within 2 years of starting RFA, then looked at relapses and rates of return to CR-D and CR-IM after more therapy.

One year after RFA therapy, the Kaplan Meier (KM) rate of invasive cancer in the 2,535 patients was 0.5%. Ten years after the start of treatment, the KM cancer rate was 4.1%, with a crude incidence rate of 0.52 per 100 patient-years. After 2 years of RFA, CR-D was 88% and CR-IM was 62.6%.

At 8 years, the KM relapse rates were 5.9% from CR-D and 18.7% from CR-IM. Most relapses happened in the first 2 years.

"Our study confirms durable reversal of dysplasia and BE with RFA, which reduces cancer risk by more than 90% compared to historical control data of 6-19% per annum," the authors wrote.

Despite advances in diagnosis and treatment for esophageal adenocarcinoma, there has been only small improvement in 5-year survival over the past 40 years, the authors note. Meanwhile, the incidence of continues to rise in the Western world.

Researchers look for minimally invasive solutions

Surgery removing the esophagus and lymph node clearance had been the standard for high-grade dysplasia, the authors wrote. It is still the intervention of choice for patients with locoregional disease, but it comes with high morbidity and mortality rates.

This has spurred researchers to look for a minimally invasive solution focused on organ preservation to treat early disease and avoid surgical side effects but also to deliver a cure, according to the authors.

Shria Kumar, MD, assistant professor in the Division of Digestive and Liver Diseases at University of Miami Miller School of Medicine, told this publication, "Endoscopic ablation of dysplasia or intramucosal cancer is a mainstay of Barrett's treatment."

She noted the importance of the 10-year time period as the initial studies that established ablation evaluated outcomes within 1-3 years, and more recent data show 5-year favorable outcomes.

Citing a study from the New England Journal of Medicine (2009 May;360[22]:2277-88), Dr. Kumar said, "The present study's cohort developed cancer at rates similar to one of the earlier U.S.-based cohorts of Barrett's patients, suggesting that we can draw some parallels."

She pointed out notable characteristics in the U.K. cohort: "The majority of participants were male and Caucasian; 80% of had high-grade dysplasia or early cancer upon enrollment and long-segment Barrett's."

That difference is important when thinking about how this applies to a more diverse U.S. population, she said, or even patients who don't have high-grade dysplasia or early cancer when they enroll.

"It's also important to point out that individuals with low-grade dysplasia were included in this U.K.-based study. There has been evidence that persons in Europe with low-grade dysplasia have higher rates of progression than persons in the U.S. with low-grade dysplasia."

Dr. Kumar said this may be attributable to differences in the way pathologists practice in the two countries or in endoscopists' treatment patterns. U.S. guidelines agree that ablation can be used in select persons with low-grade dysplasia, she said, but it's an area that needs further study.

"Overall, though, this is a really important study of real-time data showing that ablation is impacting cancer rates in a positive way and that, in select patients, we can really decrease the risk of invasive cancer by endoscopic eradication therapies," Dr. Kumar said.

Two coauthors have received grants from Medtronic and Pentax Medical. The other authors have declared no relevant financial relationships. Dr. Kumar reports no relevant financial relationships. ■

Interview with Dr. John M. Inadomi: Inside the 2022 DDW® Presidential Plenary

This year's plenary will focus on action items to eradicate health disparities in GI.

The 2022 AGA Presidential Plenary at Digestive Disease Week® (DDW) is designed to highlight timely and high-impact research as it pertains to AGA and the global gastroenterology community. This year's plenary will feature a series of invited speaker talks on the ways to integrate diversity and inclusion into the field of gastroenterology and hepatology.

Dr. Inadomi

AGA President John M. Inadomi, MD, AGAF, will present his address titled "Don't Talk – Act: The Relevance of DEI to Gastroenterologists and Hepatologists and the Imperative for Action." Read our Q&A with Dr. Inadomi below for details on what you can expect from the plenary.

PICK-UPPATH/DIGITALVISION VECTORS/GETTY IMAGES

Why did you want to focus on issues around diversity, equity, and inclusion in the presidential plenary?

Most obvious is the pandemic, and the social issues the pandemic has amplified have made these issues a primary concern for AGA. The pandemic forced us to reexamine ourselves and to not assume everything we've done in the past should be done in the future. The diversity of AGA and AGA leadership is not where we want it to be. I want to use the presidential plenary as a platform to discuss race, especially, which is only one part of DEI. I can provide perspective as an Asian American experiencing a resurgence in racism, and I want to involve nationally known experts like Monica Webb Hooper who've done research on this and have fully formed ideas on how to frame the questions and talk about action items that we, as a society, should adopt. The time of reflection and awareness has passed, the time of simply providing awareness is past. Society needs to adopt action items to address and combat racism.

Later in the plenary, I'm pleased to be joined by Dr. Byron Cryer and Dr. Sandra Quezada who will talk about how they created/developed the AGA Equity Project and their work to implement it.

What do you want attendees to take home from these various talks?

We hear a lot of talk about DEI, I hear a lot about awareness, a lot of talk about education. I asked the presidential plenary speakers to move beyond that to provide action items that AGA and its members can implement to reduce disparities in health outcomes. I hope that we will be able to measure these outcomes and see improvement over time coming out of the interventions proposed during this session.

Why did you choose disparities in CRC, liver disease, and IBD specifically?

I feel like these are core parts of gastroenterology and hepatology. So much of the disparities we see in colon cancer are a microcosm of the disparities that exist across the spectrum of GI and liver disease. They illustrate the problems with access and utilization. Disparities in CRC outcomes are exacerbated by the pandemic. I chose liver disease because it's another area where racial disparities exist and are exacerbated by the pandemic. All three are core services provided by gastroenterologists and hepatologists and represent areas where racism has caused disparities in outcomes. Greatly magnified by the pandemic.

Why is the Association of Black Gastroenterologists and Hepatologists important?

It's important for me to listen to people who are the target of racism and hear how they want AGA to address their concerns. I want a better understanding of why ABGH was formed and why now. I want to hear what they hope to achieve and how they believe the AGA can help.

The full AGA Presidential Plenary line-up

We hope you'll join us for the AGA Presidential Plenary, taking place Monday, May 23, at 10 a.m. PT during DDW. In addition to Dr. Inadomi's keynote address, presentations will include:

- AGA Julius Friedenwald Recognition of Timothy Wang
- AGA Equity Project: Accomplishments and What Lies Ahead
- The Genesis and Goals of the Association of Black Gastroenterologists and Hepatologists (ABGH)
- What We Need to Overcome Racial and Ethnic Barriers to Engage in Clinical Trials
- Reducing Disparities in Colorectal Cancer
- Reducing Disparities in Liver Disease
- Reducing Disparities in IBD ■

Apply now to become an AGA Fellow

Applications are now open for the 2023 AGA Fellowship cohort. AGA is proud to formally recognize its exemplary members whose accomplishments and contributions demonstrate a deep commitment to gastroenterology through the AGA Fellows Program.

Those in clinical practice, education, or research (basic or clinical) are encouraged to apply today.

Longstanding members who apply and meet the program criteria are granted the distinguished honor of AGA Fellowship and receive the following:

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- An official certificate and pin denoting your status.
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Hard-to-see lesions play a big role

Polyp *from page 1*

limited, wrote Joseph C. Anderson, MD, of the Geisel School of Medicine at Dartmouth, Hanover, N.H., and colleagues.

"A unique challenge for endoscopists is that serrated polyps exhibit characteristics that can make them more difficult to detect than conventional adenomas. Thus, it is not surprising that several studies have demonstrated a wide variation in serrated polyp detection rates." Even so, improved detection and resection of these polyps would likely improve CRC prevention, they noted.

The researchers reviewed data from the New Hampshire Colonoscopy Registry to explore the association between clinically significantly serrated polyp (CSSP) detection rates and subsequent PCCRC risk.

The study population included 19,532 patients with follow-up events at least 6 months after an index colonoscopy. Of these, 128 cases of CRC were diagnosed at least 6 months after an index exam. CSSP was defined as any sessile serrated polyp, traditional serrated adenoma, or any large hyperplastic polyp (> 1 cm) or proximal hyperplastic polyp > 5 mm. The exams were performed by 142 endoscopists, 92 of whom were gastroenterologists. The 50 nongastroenterologists included general surgeons, colorectal surgeons, and family practitioners.

The primary outcome was PCCRC, defined as any CRC diagnosis 6 months or longer after an index exam. Clinically significant serrated polyp detection rate (CSSDR) was determined by dividing the total number of complete screening exams with adequate prep and at least one CSSP by the total number of complete exams with adequate prep. CSSDR was divided into tertiles of less than 3%, 3% up to 9%, and 9% or higher.

"These data support our suggestion that endoscopists, even those with an ADR of 25% or higher, calculate their SDR at least once, a recommendation supported by a recent review."

Overall, the risk for PCCRC 6 months or more after an index exam was significantly lower for exams performed by endoscopists with detection rates of 3% up to 9% and for those with detection rates of 9% or higher compared to those with detection rates below 3% (hazard ratios 0.57 and 0.39, respectively).

Significantly more gastroenterologists were in the higher CSSDR categories compared to nongastroenterologists (P = .00005). The percentages of gastroenterologists in the three tertiles from lowest to highest detection were 15.2%, 50.0%, and 34.8%; compared to 46%, 44.0%, and 10.0%, respectively, for nongastroenterologists.

In adjusted analysis, higher detection rates were associated with lower CRC risk across all time periods.

The researchers also found higher CSSDR categories associated with lower PCCRC risk for exams by endoscopists with adenoma detection rates (ADR) of 25% or higher.

"It may be reasonable to question whether a separate serrated detection rate is needed in addition to ADR," the researchers wrote in their discussion of the findings. "These data support our suggestion that endoscopists, even those with an ADR of 25% or higher, calculate their SDR at least once, a recommendation supported by a recent review of the American Gastroenterological Association," they noted.

The study findings were limited by several factors, including the lack of information on specific endoscopic techniques, a lack of data on the molecular characteristics of the cancers, and potential residual confounding variables, the researchers noted.

However, the results were strengthened by the large number of participating endoscopists and by the longitudinal database that included detection rates for screening exams and detailed polyp pathology, they said. The results support the need for a serrated polyp detection rate benchmark to endure complete polyp detection and validate the use of CSSDR as a quality measure that adds to the knowledge of both colonoscopy quality and the role of the serrated pathway in colorectal cancer, they concluded.

Serrated pathway serves as predictor

The current study is an important addition to the knowledge of colorectal cancer risk, Atsushi Sakuraba, MD, PhD, associate professor of medicine at the University of Chicago, said in an interview.

"In addition to the conventional adenoma pathway, the serrated pathway has been recognized to account for a significant portion of colorectal cancer, but whether detection of serrated polyps [is] associated with reduction of CRC remains unknown," he said.

Dr. Sakuraba said he was not surprised by the study findings. Given that the serrated pathway is now considered to account for approximately 10%-20% of all CRC cases, higher detection rates should result in lower risk of CRC, he noted.

The findings support the value of CSSDR in clinical practice, said Dr. Sakuraba. "The study has shown that a clinically significant serrated polyps detection rate of 3% was associated with lower postcolonoscopy CRC, so endoscopists should introduce this to their practice in addition to adenoma detection rates," he said.

However, Dr. Sakuraba acknowledged the limitations of the current study and emphasized that it needs to be reproduced in other cohorts. Prospective studies might be helpful as well, he said.

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

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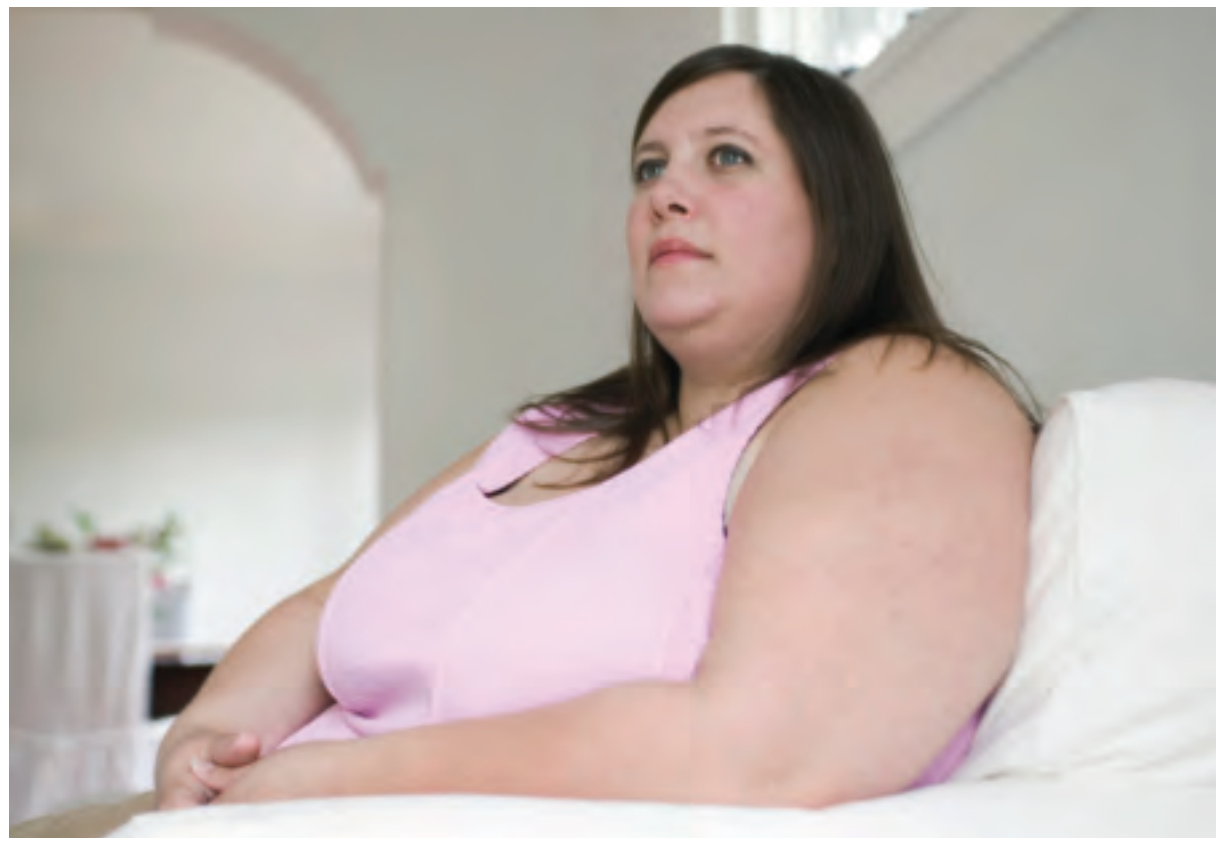
Excess weight over lifetime hikes risk for CRC

BY MARCIA FRELLICK
MDedge News


GRAVITY IMAGES/DIGITALVISION

Excess weight over a lifetime may play a greater role in a person's risk for colorectal cancer (CRC) than previously thought, according to new research.

In their paper published online March 17 in JAMA Oncology (2022. doi: 10.1001/jamaoncol.2022.0064), the authors liken the cumulative effects of a lifetime with overweight or obesity to the increased risk of cancer the more people smoke over time.

This population-based, case-control study was led by Xiangwei Li, MSc, of the division of clinical epidemiology and aging research at the German Cancer Research Center in Heidelberg.

It looked at height and self-reported weight documented in 10-year increments starting at age 20 years up to the current age for 5,635 people with CRC compared with 4,515 people in a control group.

Odds for colorectal cancer increased substantially over the decades when people carried the excess weight long term compared with participants who remained within the normal-weight range during the period.

Coauthor Hermann Brenner, MD, MPH, a colleague in Mr. Li's division at the German Cancer Research Center, said in an interview that a key message in the research is that "overweight and obesity are likely to increase the risk of colorectal cancer more strongly than suggested by previous studies that typically had considered body weight only at a single point of time."

"With the recent rise in young-onset colorectal cancer since the 1990s there has been a lot of interest in looking at whether obesity is a major contributor to that rising trend."

The researchers used a measure of weighted number of years lived with overweight or obesity (WYOs) determined by multiplying excess body mass index by number of years the person carried the excess weight.

They found a link between WYOs and CRC risk, with adjusted odds ratios increasing from 1.25 (95% confidence interval, 1.09-1.44) to 2.54 (95% CI, 2.24-2.89) from the first to the fourth quartile of WYOs, compared with people who stayed within normal-weight parameters.

The odds went up substantially the longer the time carrying the excess weight.

"Each [standard deviation] increment in WYOs was associated with an increase of CRC risk by 55% (adjusted OR, 1.55; 95% CI, 1.46-1.64)," the authors wrote. "This OR was higher than the OR per SD increase of excess body mass index at any single point of time, which ranged from 1.04 (95% CI, 0.93-1.16) to 1.27 (95% CI 1.16-1.39)."

Dr. Brenner said that, although this study focused on colorectal cancer, "the same is likely to apply for other cancers and other chronic diseases."

Prevention of overweight and obesity to reduce burden of cancer and other chronic diseases "should become a public health priority," he said.

Preventing overweight in childhood is important

Overweight and obesity increasingly are starting in childhood, he noted, and may be a lifelong burden.

Therefore, "efforts to prevent their development in childhood, adolescence, and young adulthood are particularly important," Dr. Brenner said.

The average age of the patients was 68 years in both the CRC and control groups. There were more men than women in both groups: 59.7% were men in the CRC group and 61.1% were men in the control group.

"Our proposed concept of WYOs is comparable to the concept of pack-years in that WYOs can be considered a weighted measure of years lived with the exposure, with weights reflecting the intensity of exposure," the authors wrote.

Study helps confirm what is becoming more clear to researchers

Kimmie Ng, MD, MPH, a professor at Harvard Medical School and oncologist at Dana-Farber Cancer Institute, both in Boston, said in an interview that the study helps confirm what is becoming more clear to researchers.

"We do think that exposures over the life course are the ones that will be most strongly contributing to a risk of colorectal cancer as an adult," she said. "With obesity, what we think is happening is that it's setting up this milieu of chronic inflammation and insulin resistance, and we know those two factors can lead to higher rates of colorectal cancer development and increased tumor growth."

She said that the ideal, but impractical, way to do a study like this would be to follow healthy people from childhood and document their weight over a lifetime. Instead, this case-control study's protocol asked people to recall their weight at different time periods, which is a limitation and could lead to recall bias.

But the study is important, Dr. Ng said, and it adds convincing evidence that addressing the link between excess weight and CRC and chronic diseases should be a public health priority.

"With the recent rise in young-onset colorectal cancer since the 1990s there has been a lot of interest in looking at whether obesity is a major contributor to that rising trend," Dr. Ng noted. "If obesity is truly linked to colorectal cancer, these rising rates of obesity are very worrisome for potentially leading to more colorectal cancers in young adulthood and beyond."

The study authors and Dr. Ng report no relevant financial relationships.

The new research was funded by the German Research Council, the Interdisciplinary Research Program of the National Center for Tumor Diseases, Germany, and the German Federal Ministry of Education and Research. ■

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

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