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Courtesy Dr. Rahul Dalal

Dr. Rahul Dalal's results suggest that, compared with anti–tumor necrosis factor therapy, vedolizumab has a lower risk of CDI.

Vedolizumab does not increase risk of *C. diff* infection in UC

BY BRANDON MAY

MDedge News

Vedolizumab does not seem to increase the risk of *Clostridioides difficile* infection (CDI), compared with anti–tumor necrosis factor (TNF) therapies in biologic-naive patients with ulcerative colitis (UC), despite concerns that the gut-selective monoclonal antibody treatment may increase gastrointestinal infections at a greater rate than other biologics in this patient population.

Perturbations of the gut microbiota that occur in inflammatory bowel disease (IBD) predispose patients to CDI. Given that treatment with monoclonal antibody vedolizumab exerts an inhibitory action on lymphocyte trafficking to the intestines, questions have been raised on whether this action could increase the risk of CDI in an already vulnerable population.

In patients with UC, the incidence of CDI typically confers a higher risk of adverse outcomes. Unfortunately, CDI is a common complication associated with IBD that can lead to disease

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Sleeve, RYGB reduce liver fat in type 2 diabetes

'Compelling evidence' for clinicians

BY JIM KLING

MDedge News

Both Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are effective at improving hepatic steatosis in type 2 diabetes patients, according to a new analysis of a randomized, controlled trial.

Both procedures resulted in near elimination of liver fat 1 year after the surgery, but the effect on liver fibrosis was less clear. The authors called for more research to examine longer-term effects on fibrosis.

"Both gastric bypass and the sleeve had complete resolution of the liver fat based on their MRI findings. That's impressive," said Ali Aminian, MD, who was asked to comment on the study. Dr. Aminian is a professor of surgery and director of the Bariatric & Metabolic Institute at the Cleveland Clinic.

About 25% of the general population, and about 90% of people with type 2 diabetes and obesity have nonalcoholic fatty liver disease (NAFLD), which can lead to liver failure or hepatocellular carcinoma. Hepatic steatosis can combine with obesity, insulin resistance, and inflammation to heighten the risk of

See **RYGB** · *page 23*

GERD: Upper endoscopy may reduce GI cancer mortality

BY JIM KLING

MDedge News

Among individuals with gastroesophageal reflux disease (GERD), a negative upper endoscopy is associated with decreased risk in incidence and mortality from gastrointestinal cancer. The benefit persisted through 5-10 years following the procedure.

The finding is similar to the survival benefit seen with colonoscopies and colorectal cancer, and may be attributable to endoscopic treatment of premalignant lesions.

"The relatively high incidence rate of upper gastrointestinal cancer in

See **GERD** · *page 6*

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LETTER FROM THE EDITOR

The power of physician advocacy

February is National Cancer Prevention Month. With approximately 4.8 million new cases and 3.4 million deaths worldwide annually, GI cancers represent roughly a quarter of the global cancer incidence and over a third of all cancer-related deaths, according to one study (Gastroenterology. 2020;159[1]:335-49).

In this month's issue of GI & Hepatology News, we feature timely content relevant to prevention and early detection of GI cancers, which remains a central focus of our clinical and endoscopic practice as gastroenterologists. This includes important studies that demonstrate the value of upper endoscopy in reducing GI cancer mortality, illustrate the potential promise of artificial intelligence in improving early detection of gastric cancer, and link adenoma detection rate to long-term survival in patients who undergo colorectal cancer screening with flexible sigmoidoscopy. We also report on a focused update from the U.S. Multi-Society Task Force on CRC, which thoughtfully reviews the data supporting a shift in the age of initiation of average-risk CRC screening from 50 to 45 years.

On the policy front, AGA and its partners have worked tirelessly for many years to eliminate financial barriers to CRC screening through national advocacy efforts. These efforts resulted in closure of the so-called Medicare "colonoscopy loophole" through legislation included in the COVID-19 relief bill – as a result, out-of-pocket costs for patients undergoing a screening colonoscopy that results in polypectomy are disallowed as of January 2022. In response to multi-society advocacy efforts, the Biden administration issued new guidance in January that requires private insurers to provide coverage without cost sharing for a follow-up colonoscopy after a positive stool-based CRC screening test for insurance coverage plan or policy years starting on or after May 31, 2022. Removing these financial barriers to care is particularly critical to efforts to improve CRC screening rates among medically underserved communities.

Dr. Adams

Removing these financial barriers to care is particularly critical to efforts to improve CRC screening rates among medically underserved communities.

These achievements highlight the power of physician advocacy in inspiring policy changes that directly improve the health and well-being of our patients. I encourage you to visit the AGA website (https://gastro.org/advocacy-and-policy/get-involved/) to learn how you can contribute to ongoing advocacy efforts.

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

Busting three myths about planned giving

Gifts to charitable organizations, such as the AGA Research Foundation, in your future plans can ensure that your support for our mission to fund young investigators will continue even after your lifetime. See these three fast facts about planned giving.

- **Planned gifts are complicated and confusing.** They don't have to be. There are many types of planned gifts: Most are simple and affordable, like a gift in your will or living trust. You just need to find the one that best meets your needs.
- **Wills are only for older adults.** Having a plan for the future is important – no matter your age. A will makes your wishes known and provides your loved ones with peace of mind.
- **Planned gifts are only for the wealthy.** Anyone can make a planned gift. Gifts of all sizes make a difference at the AGA Research Foundation. In fact, you may even be able to make a bigger impact than you thought possible when you make a planned gift.

For 2022, consider including a gift to the AGA Research Foundation in your will. You will help spark future discoveries in GI.

Want to learn more about including a gift to the AGA Research Foundation in your plans? Visit our website at https://gastro.planmylegacy.org or contact us at foundation@gastro.org. ■

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GI & HEPATOLOGY NEWS

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Single-use duodenoscope found cost effective

Model-D, HLD, culture-and-quarantine (CQ), and ethylene oxide sterilization (ETO). The results came from a simulated cohort of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) to treat choledocholithiasis.

Although EXALT was the costliest option and HLD the cheapest, EXALT produced the most quality-adjusted life-years (QALYs) and allowed the hospital to decrease net costs, and sensitivity analysis showed that it was a better option than HLD over a range of willingness-to-pay values.

"When evaluating technologies based on cost-effectiveness and additionally in the context of TPT [transitional passthrough] or NTAP [new technology add-on payment], the EXALT approach meets typically used cost-effectiveness thresholds compared to all other evaluated strategies and should be considered for standard practice," wrote the authors, who were led by Ananya Das, MD, of the Arizona Centers for Digestive Health, Gilbert. The study was published in Techniques and Innovations in Gastrointestinal Endoscopy (2021 Oct. doi: 10.1016/j.tige.2021.09.007).

"The EXALT approach meets typically used cost-effectiveness thresholds compared to all other evaluated strategies and should be considered for standard practice."

Duodenoscope contamination has resulted in outbreaks of various multidrug-resistant organisms in hospital settings, which has led to the publication of various reprocessing guidelines. Although many hospitals have adopted HLD protocols, others use additional or alternative reprocessing methods such as CQ or ETO. Despite these efforts, a recent Food and Drug Administration study found that 1.9%-22% of samples taken from duodenoscopes tested positive for bacteria of concern, such as pathogens. Those and other findings have led some to suggest that it would be best to move away from HLD, and instead employ sterilizable or disposable endoscopes.

In another study, The EXALT Model-D (Boston Scientific) had been shown to be a good alternative to standard reusable duo-

Continued on following page

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Continued from previous page

denoscopes (Clin Gastroenterol Hepatol. 2020 Aug;18[9]:2108-17.e3).

The researchers used a Markov-model to determine the cost-effectiveness of EXALT Model-D against other approaches in a simulated cohort. They found that EXALT Model-D created the most QALYs (21.9265) at the highest cost ($3,000), and HLD the fewest QALYs (21.8938) at the lowest cost ($962). Compared with HLD, the incremental cost-effectiveness ratio (ICER) of EXALT was $62,185, and $38,461 for ETO gas sterilization. CQ was dominated, indicating that it had a higher cost but was not more effective than HLD.

The researchers conducted a subanalysis of ERCP and Medicare patients to consider the recently approved TPT payment and the NTAP, in both hospital outpatient and inpatient settings. With TPT, EXALT had no cost after reimbursement, with a net saving of $962 per patient when compared with HLD, plus an increase in 0.033 QALYs (0.15%). The other procedures cost more and were less effective. With NTAP, EXALT had a net cost of $323 versus HLD, with a similar QALY benefit.

A Monte Carlo analysis of EXALT versus HLD found reductions in duodenoscope infection-related ICU admission (relative risk reduction, 0.996; 95% confidence interval, 0.936-1.0; number needed to treat, 79; 95% CI, 67-95) and death (RRR, 0.973; 95% CI, 0.552-0.998; number needed to treat, 556; 95% CI, 350-997).

In willingness-to-pay estimates from $50,000 to $100,000, EXALT was cost effective in 67.28% of trials with ICER under $100,000 per QALY.

The study did not consider medicolegal costs, which could lead to an underestimation of EXALT's cost-effectiveness. The study also relied on available published information to determine cost per patient of hospital outbreaks in the United States and Europe since 2012, but the authors did not include costs of administrative sanctions, litigation, and poor publicity due to inconsistencies in the literature.

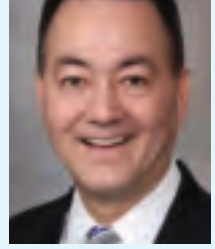
Duodenoscope contamination has resulted in outbreaks of various multidrug-resistant organisms in hospital settings, which has led to the publication of various reprocessing guidelines.

"While more research is needed to understand and quantify the determinants of the natural history after exposure to contaminated duodenoscopes, such as the risk of transmission and the subsequent development of serious clinical infections, this economic analysis demonstrates an approach using EXALT Model-D is cost effective in the U.S. health care system when compared to the currently utilized strategies of duodenoscope reprocessing," the researchers concluded.

The study did not receive any funding. One of the authors is an employee and stockholder of Boston Scientific, which manufactures and markets EXALT. The other two authors have consulted for Boston Scientific. ■

STURTI/GETTY IMAGES

Consider for a moment: The single-use duodenoscope (SUD) represents a revolutionary approach to duodenoscope infection control. Who, even 10 years ago, would have imagined that a disposable duodenoscope would even be technically achievable, much less economically feasible? Notwithstanding, determining how to incorporate such a revolutionary new technology and its associated capital and recurring costs can be every bit as complex and challenging as conceiving and developing the SUD. The authors provide insights into answering these questions through Markov modeling, comparing cost-effectiveness of SUDs to traditional duodenoscopes (TD) using available data on TD and SUD performance, and extrapolating from nonendoscopic infection management data.



Dr. Martin

This analysis is helpful because it demonstrates that, despite SUD cost approaching $3,000, Centers for Medicare & Medicaid Services inpatient and outpatient cost-defrayment payments may result in SUDs being cost effective within limits and assumptions the study incorporates. This information is also timely, because these CMS subsidies are guaranteed only through mid-2022 for Medicare inpatients and 2023 for Medicare outpatients.

Though useful and timely, this study does make assumptions that narrow its applicability to real-world endoscopic retrograde cholangiopancreatography (ERCP). Clinically, it considers only patients with uncomplicated common bile duct stones. While choledocholithiasis is the indication for ERCP in the majority of patients, over 40% of ERCPs in the United States are performed for other, often more complex applications. While most procedures in the referenced studies were performed by high-volume ERCP proceduralists, a substantial proportion of ERCPs are performed by lower-volume ERCP proceduralists, who actually perform a substantial proportion of straight-forward ERCPs addressing uncomplicated choledocholithiasis.

This study focuses cost implications on CMS Transitional Pass-through (TPT) and New Technology Add-On Payment (NTAP) subsidies available only for Medicare inpatients and outpatients, respectively. These reimbursements are set to expire in 2022 (inpatients) and 2023 (outpatients). What will happen after that? Also, the amount of TPT and NTAP cost defrayments are institution-dependent, because cost-to-charge ratio (CCR), an important factor in calculating these subsidies, varies substantially between institutions and regions. In the future, how will the cost of SUDs be incorporated into the hospital business model when TPT and NTAP are over?

SUDs are a technological marvel and a remarkable advance in endoscopic infection control. But innovations in medical technology are expectedly accompanied by new operational challenges: How to incorporate them into day-to-day practice, and develop a business model that avails valuable new resources to patients. Such operational challenges require as much heavy lifting as the technological innovation needed to produce innovative devices like SUDs. The authors' vision and effort in ideating and executing this study gives us a head-start on this path by helping us to imagine what is possible.

John A. Martin, MD, is associate professor and consultant at the Mayo Clinic, Rochester, Minn. He is a former member of the editorial board for GI & Hepatology News, and has no relevant conflicts to disclose.

Reducing cancer mortality

GERD *from page 1*

patients with GERD indicates that a one-time upper endoscopy may be beneficial," wrote the authors, who were led by Dag Holmberg, MD, PhD, of the department of molecular medicine and surgery at the Karolinska Institutet and Karolinska University Hospital,

"Upper endoscopy may be beneficial for patients with GERD, but to make upper endoscopy screening more cost beneficial at its initiation, the target group may be limited to include patients at highest risk of cancer."

both in Stockholm. The study was published in Gastroenterology (2021 Oct. doi: 10.1053/j.gastro.2021.10.003).

GERD is the most frequent reason patients undergo an upper endoscopy, but the results are often negative. It is generally a benign condition, but can lead to Barrett's esophagus, as well as esophageal and gastric cardia adenocarcinoma. Upper endoscopy can identify other esophageal cancers like gastric

NEBARI/THINKSTOCK

noncardia cancer and duodenal cancer, which may cause dyspepsia or GERD-like symptoms.

To determine the potential benefit of upper endoscopy, the researchers conducted a population-based, four-nation cohort study that included 1,062,740 individuals with GERD in Denmark, Finland, Norway, and Sweden. The data were gathered from national patient registries, cancer registries, and cause of death registries. The study encompassed data from 1979 through the end of 2018.

The median age was 58 years, and 52% of participants were women.

The researchers defined a negative endoscopy as no diagnosis of gastrointestinal cancer within 6 months of the procedure; 69.3% of procedures were negative.

During the follow-up period, 0.34% of participants developed and 0.27% died of upper gastrointestinal cancer. Among those with negative endoscopies, 0.23% developed and 0.22% died from upper gastrointestinal cancer.

Participants with a negative endoscopy had a lower risk of being diagnosed with upper gastrointestinal cancer during the follow-up period (adjusted hazard ratio, 0.45; 95% confidence interval, 0.43-0.48). The reduction in risk was similar across age sexes and age groups, but among procedures performed after 2008, the risk reduction was even higher (aHR, 0.34; $P < .001$).

The effect was strongest in the first year after the procedure, but it persisted out to 5 years before returning to baseline risk levels.

A negative endoscopy was also associated with decreased mortality risk from upper gastrointestinal cancer versus those who hadn't had an endoscopy (aHR, 0.39; 95% CI, 0.37-0.42). The protective value continued for at least 10 years.

Esophageal adenocarcinoma developed in 0.12% of participants, and 0.10% died of the disease. Among those with a negative endoscopy, 0.09% developed adenocarcinoma, and 0.07% died (aHR vs. no upper endoscopy, 0.33; 95% CI, 0.30-0.37).

The rapid return to baseline risk was notable, and different from what occurs after negative colonoscopies. However, new tumors can readily form within 1 year, and the risk may reflect early malignant or premalignant lesions that were missed during the procedure.

In fact, a meta-analysis found that 11.3% of upper gastrointestinal cancers had escaped detection during an endoscopy in the previous 3 years before diagnosis (Endosc Int Open. 2014 Jun;2[2]:E46-50), and case reviews of patients diagnosed with gastrointestinal cancer soon after an upper endoscopy usually reveal suspicious or indeterminate results that the endoscopist or pathologist missed.

Quality indicators for upper endoscopy include procedure time, rate of targeted biopsies, and computer-aided detection, but it isn't clear what impact these measures have on outcomes. However, the greater risk reduction found with endoscopies performed more recently suggests that newer quality indicators and technological improvements may be improving outcomes.

The relatively low incidence of esophageal and gastric cancer in Western countries has discouraged widespread adoption of endoscopic screening, but the researchers point out that the risk of gastrointestinal cancer among individuals with GERD is similar to the risk of colorectal cancer in the 60-69 age group in the United States, for whom colonoscopy is recommended.

"The present study indicates that upper endoscopy may be beneficial for patients with GERD, but to make upper endoscopy screening more cost beneficial at its initiation, the target group may be limited to include patients at highest risk of cancer. Such previous cost-effectiveness studies have indicated that endoscopy is cost effective in men at aged 50 years or older with chronic GERD," the authors wrote.

The study was funded by Swedish Research Council and Swedish Cancer Society. The authors disclosed no relevant conflicts of interest. ■

This study from Holmberg and colleagues has the potential to revolutionize future clinical guidelines determining endoscopic investigations for GERD patients.

Dr. Coleman

The cohort for analysis is staggering in magnitude: The authors analyzed real-world data from over 1 million participants with GERD in four Scandinavian databases. The results show strong and precise reductions in both risk and mortality from upper gastrointestinal cancer in the whole cohort. This reduction was consistent across all subgroup and sensitivity analyses.

These findings are important as GERD alone does not necessarily warrant an upper endoscopy investigation in current practice. This study provides strong evidence that a one-off endoscopic investigation in patients with GERD could bring meaningful opportunities for early detection of esophageal and gastric cancers – and in turn lead to fewer patients dying from these tumors. The immediacy of the return for investment is also impressive; with the risk reduction being strongest in the first few years of follow-up.

The elusive next step, as highlighted by the authors, is to ensure implementation of endoscopic screening can be done in a cost-effective manner. This is even more important because many health care systems across the world struggle with endoscopy capacity during the COVID-19 pandemic.

Helen Coleman, PhD, BSc(Hons), is a professor of cancer epidemiology at Queen's University Belfast (Northern Ireland); joint deputy director of the Northern Ireland Cancer Registry; a Cancer Research UK Fellow; and a visiting scientist with the Fitzgerald Lab at the University of Cambridge (England). She has no conflicts.

Corrections

An article comparing combinations of imaging and nonimaging approaches among patients with nonalcoholic steatohepatitis ("MRE plus FIB-4 beats FAST for detecting NASH-related fibrosis," November 2021, p. 1) inadvertently misstated the percentages in each cohort who were experiencing significant fibrosis. The sentence should have read: "Significant fibrosis was found in 66.2% of the Yokohama cohort and 29.5% of the UCSD cohort." ■

* * *

In an article comparing endoscopic submucosal dissection with cap-assisted endoscopic mucosal resection ("ESD vs. cEMR: Rates of complete remission in Barrett's compared," January 2022, p. 1), there was an inadvertent misstatement of lesion sizes in the boxed commentary. The sentence, on p. 9, should have read: "However, ESD is more effective for achieving CRD and may be preferable for lesions greater than 15 mm or lesions where superficial submucosal invasion is suspected and providing an accurate histopathologic specimen would help direct appropriate oncologic therapy." ■

Smoking and alcohol raise risk of second cancer in squamous cell carcinoma

BY HEIDI SPLETE
MDedge News

Field cancerization and subsequent second cancer in squamous cell carcinoma (SCC) patients was significantly associated with cigarette and alcohol use, based on data from more than 300 individuals.

Cigarette and alcohol use are established risk factors for SCCs of the esophagus, head, and neck, Manabu Moto, MD, of Kyoto University and colleagues wrote. "In addition, squamous cell carcinoma and squamous dysplastic epithelium develop multifocally in these organs," in a phenomenon known as field cancerization, but the interaction of multiple dysplastic epithelium with other factors, notably whether cessation of cigarette and alcohol use would reduce risk of SCC, has not been well studied.

"We believe that our data will be useful to establish a prevention and surveillance strategy for cancer survivors, because the overall prognosis of esophageal cancer and head and neck cancer is still poor," with a 5-year survival rate of less than 20%

In a study published in Gastro Hep Advances (2021 Oct 21. doi: 10.1016/j.gastha.2021.10.005), the researchers identified 331 adults with newly diagnosed superficial esophageal SCC who underwent endoscopic resection, and 1,022 healthy controls. Field cancerization was based on the number of Lugol-voiding lesions (LVLs) per endoscopic view according to three groups: grade A, 0 LVLs; grade B, 1-9; or grade C, at least 10. The primary study outcome was a measure of risk factors for the development of LVLs.

"Multiple LVLs are closely associated with inactive aldehyde dehydrogenase 2 (ALDH2) and field cancerization," the researchers wrote. Before assessing their human subjects, they used a mouse model to investigate whether alcohol intake and abstinence would affect acetaldehyde-induced DNA damage to the esophageal epithelium among individuals with ALDH2 dysfunction.

The researchers found that DNA damage, measured by acetaldehyde-derived DNA adduct levels (via N^2-ethylidene-dG), accumulated with alcohol consumption over time, but decreased with alcohol cessation in the mouse model.

For the human part of the study, participants completed a lifestyle survey at entry, with questions about alcohol consumption history, alcohol flushing response, smoking, consumption of high-temperature foods, and consumption of green and yellow vegetables and fruit.

Drinking status was divided into five groups: never/rarely (of less than 1 unit/week), light (1-8.9 units/week), moderate (9-17.9 units/week), heavy (18 or more units/week), and ex-drinker, with 1 unit defined as 22 g of ethanol. Smoking was divided into three groups: never (0 pack-years), light (less than 30 pack-years), and heavy (30 or more pack-years). Patients were given educational materials at study entry about the importance of alcohol and smoking cessation, as well as verbal advice to cease these behaviors.

Participants underwent endoscopic surveillance at 3-month intervals for up to 6 months following endoscopic resection.

Overall, increased alcohol consumption was associated with increased risk in development of LVL across all LVL grades; higher grades of LVLs were positively associated with high-intensity alcohol consumption, smoking, flushing, and high-temperature foods, and negatively associated with eating vegetables and fruit.

The risk of LVL grade progression was most strongly associated with increased alcohol consumption and with reported flushing. "The greatest risk was observed in the patients with flushing reactions who consumed an average of 30 units per week in grade C LVL," with an odds ratio of 534, compared with healthy controls. "Since flushing reaction is caused by accumulation of acetaldehyde due to ALDH2 deficient, our result also means that acetaldehyde is a strong carcinogen in field cancerization."

Secondary outcomes included the incidence of second primary esophageal SCC and head/neck SCC; these were significantly more prevalent in patients with grade C LVL (cumulative 5-year incidence of 47.1% for ESCC and 13.3% for head and neck SCC). However, alcohol and smoking cessation significantly reduced the development of second primary esophageal SCC (adjusted hazard ratios, 0.47 for alcohol and 0.49 for smoking).

The study findings were limited by several factors including the lack of randomization to noncessation and cessation groups and the inclusion of cancer patients, but not long-term cancer survivors, the researchers noted.

"We believe that our data will be useful to establish a prevention and surveillance strategy for cancer survivors, because the overall prognosis of esophageal cancer and head and neck cancer is still poor," with a 5-year survival rate of less than 20%, and the results highlight the need to educate cancer survivors on the value of smoking and alcohol cessation, they added.

The study was supported by the National Cancer Center Research and Development Fund 36 by the Ministry of Health, Labour, and Welfare of Japan. The researchers had no financial conflicts to disclose. ■

In this large, prospective, multicenter Japanese study published in the December 2021 issue of Gastro Hep Advances, alcohol and/or smoking cessation for 5 or more years was found to reduce the risk of field cancerization in patients with superficial esophageal squamous cell carcinoma (ESCC). Multiple lesions that are identified by lack of staining of squamous epithelium of the esophagus with Lugol iodine (Lugol-voiding lesion) are known as field cancerization effect. The investigators found that, following endoscopic resection of first primary ESCC (n = 331), alcohol cessation (adjusted hazard ratio, 0.47; 95% confidence interval, 0.26-0.85) and cigarette smoking cessation (AHR, 0.49; 95% CI, 0.26-0.91) reduced the rate of development of second primary ESCC.

This study highlights the magnitude of impact that known environmental exposures can have on the development and prognosis in ESCC. The investigators found that heavy drinking was almost 6.6 times, and heavy smoking was 2.1 times, as prevalent in individuals with high-grade esophageal epithelial dysplasia identified on Lugol iodine staining. In a mouse model, they showed that acetaldehyde, an established carcinogen produced during ethanol metabolism, which is also a compound found in cigarette smoke, induces DNA damage in the esophageal epithelium. According to this study, individuals with superficial ESCC and an inactive aldehyde dehydrogenase 2 enzyme are at higher risk for expansion and progression of esophageal dysplastic epithelium. A flushing reaction following ethanol ingestion is a marker of inactive aldehyde dehydrogenase in humans.


Dr. Jain


Dr. Mittal

The take-home message from this study is that alcohol and tobacco cessation for 5 years can significantly reduce the risk of second primary ESCC. Practitioners should be vigilant in counseling patients, particularly those with Lugol-voiding lesions grades B or C or those who have a flushing reaction.

Anand Jain, MD, is with the division of digestive diseases at Emory University, Atlanta. Ravinder Mittal, MD, is with the division of digestive diseases at University of California, San Diego. They declared having no relevant conflicts of interest.

High GI spending reveals research, public health need

BY WILL PASS
MDedge News

GI, liver, and pancreatic diseases cost the U.S. health care system about $120 billion per year and account for approximately 250,000 annual deaths, according to a "conservative" estimate from a recent analysis.

These figures emphasize the need for more research funding in the area, along with additional clinical and public health initiatives, reported lead author Anne F. Peery, MD, of the University of North Carolina School of Medicine, Chapel Hill, and colleagues.

"Reports detailing the burden of GI diseases are necessary for clinical research, decision making, and priority setting," the investigators wrote in Gastroenterology (2021 Oct. doi: 10.1053/j.gastro.2021.10.017). "Our aim was to describe health care use, expenditures, and research funding across GI, liver, and pancreatic diseases in the United States."

Dr. Peery and colleagues analyzed data from 14 sources, including the National Institutes of Health; the Centers for Disease Control and Prevention; the National Ambulatory Medical Care Survey; and others. GI-specific outcomes included mortality, readmissions, hospitalizations, office-based visits, and emergency department visits. The investigators also characterized trends in cancers, organ transplants, and GI endoscopy, as well as GI-specific health care costs and NIH research funding. Annual findings were presented for various periods.

Brian Strickland/University of North Carolina

"Our aim was to describe health care use, expenditures, and research funding," wrote Dr. Anne F. Peery.

Total GI health care spending was $119.6 billion in 2018, down from $135.9 billion in 2015. The top five most costly conditions were biliary tract diseases ($16.9 billion), esophageal disorders ($12.1 billion), abdominal pain ($9.5 billion), abdominal hernias ($9.0 billion), and diverticular disease ($9.0 billion). The investigators noted that medication costs were particularly high for two categories: inflammatory bowel diseases and esophageal disorders, which had prescription drug costs relative to total expenditures of 71% and 53%, respectively.

"This conservative estimate [of $119.6 billion] did not include most GI cancers and likely underestimated the costs associated with some GI conditions," the investigators noted. "For example, the Medical Expenditure Panel Survey estimate associated with GI bleeding was $300 million. In comparison, the aggregate cost of GI bleeding was more realistically $3.7 billion, as estimated using inpatient data from the National Inpatient Sample."

In 2016, the most common GI-related diagnosis in the United States was abdominal pain (15.7 million annual visits), followed by nausea and vomiting (5.0 million visits), gastroesophageal reflux disorder and reflux esophagitis (4.7 million visits), constipation (3.1 million visits), and abdominal wall/inguinal hernia (2.8 million visits).

The top three most common GI-related hospital admissions in 2018 were GI bleeding (1.3 million admissions), followed by cholelithiasis and cholecystitis (741,060 admissions), then pancreatitis (685,880 admissions). GI bleeding was also the leading cause of 30-day readmission in 2018 (84,533 readmissions).

"We found substantial numbers of GI conditions and symptoms listed in secondary positions on the discharge record," the investigators wrote. "For example, liver disease accounted for 280,645 discharges with a primary diagnosis; however, there were 13-fold as many discharges (3.6 million in 2018) with liver disease as a secondary diagnosis. Including all diagnoses captures a burden of GI disease not previously reported."

In 2018 and 2019, GI diseases and cancers caused 255,407 annual deaths. The most common noncancer deaths were caused by alcoholassociated liver disease (24,110 deaths), hepatic fibrosis/cirrhosis (20,184 deaths), and GI bleeding (9,548 deaths). Among GI-cancer–related deaths, colorectal cancer (CRC) caused the most mortalities (52,163 deaths), followed by pancreatic cancer (44,914 deaths), and hepatic/biliary cancer (44,914 deaths). The investigators noted that CRC was disproportionately common among non-Hispanic Black individuals, whereas gastric cancer was relatively high among Hispanic individuals.

"GI cancers account for a large number of diagnoses and deaths annually, with persistent disparities in incidence and mortality rates by race/ethnicity," the investigators wrote. "Racial, ethnic, and regional disparities in access to most GI endoscopy procedures exist, which suggests an unmet need for GI procedures across the United States."

A total of 22.2 million endoscopies were performed in 2019, most commonly colonoscopy (13.8 million procedures), followed by upper endoscopy (7.5 million procedures), and flexible sigmoidoscopy (379,883 procedures).

In 2020, the NIH spent $3.1 billion, or approximately 7.5% of its budget, on GI disease research. Digestive diseases captured the bulk of this spending, with $2.3 billion. In the same year, the NIH spent 10.5% of its cancer research budget on GI cancers, with the greatest proportion ($325 million) awarded to CRC research.

"Carefully examining the data in this report can help generate areas for future investigation, prioritize research funding, identify areas of unmet need or disparities, and provide an important overview of the impact of digestive and liver conditions," the investigators concluded. "We hope that others will use this report as motivation to take a deeper dive into individual diseases. There is much to learn from carefully studying existing data sources."

The study was supported by the National Center for Advancing Translational Sciences, National Institutes of Health. The investigators disclosed no conflicts of interest. ■

Flexible sigmoidoscopy adenoma detection rates linked to reduced long-term mortality

BY JIM KLING
MDedge News

Gastroenterology centers with higher adenoma detection rates (ADR) with the use of flexible sigmoidoscopy (FS) had a lower long-term colorectal cancer incidence and lower CRC mortality among its patients, according to a new study.

Detection and removal of polyps during colonoscopy screening are vital to the prevention of CRC, and previous research has shown that centers with higher detection rates are associated with lower rates of CRC diagnosis within 3-5 years after a negative screen.

In Clinical Gastroenterology and Hepatology (2020 Sep. doi: 10.1016/j.cgh.2020.09.020), researchers led by Amanda J. Cross, PhD, a professor of cancer epidemiology at Imperial College London, published an analysis of the UK Flexible Sigmoidoscopy Screening Trial, which found that FS screening between the ages 55 and 64 led to a 35% reduction of CRC incidence and a 41% reduction in CRC over a mean follow-up 17.1 years (Lancet. 2017 Apr 1;389[10076]:1299-311).

"The improved detection of adenomas at [flexible sigmoidoscopy] has a measurable impact on long-term distal CRC outcomes, even when there is infrequent colonoscopy use."

The screening program had no apparent effect on incidence and mortality of proximal cancers. The researchers speculated that this was because few patients underwent proximal examination during follow-up colonoscopy.

"Considering only 5% of participants were referred for follow-up colonoscopy and 4% were referred for surveillance, we conclude that the improved detection of adenomas at FS has a measurable impact on long-term distal CRC outcomes, even when there is infrequent colonoscopy use. It is possible that high detectors also were more adept at polypectomy than intermediate or low detectors, and achieved more complete resection of detected lesions," the authors wrote.

The researchers analyzed data from 38,550 patients who underwent screening at 14 U.K. hospitals, between 1994 and 1999. A single endoscopist was responsible for nearly all FS screens performed at each participating hospital.

The mean patient age was 60 years, and 49% were male. The researchers calculated ADRs for each center using the percentage of patients who had at least one adenoma detected during screening, which included any distal adenomas discovered during follow-up colonoscopy.

The ADR overall was 12%. The researchers used multivariate logistic regression to rank individual centers as having high (15%; five centers), intermediate (12%; four centers), or low (9%; four centers) detection rates.

There was a strong association between detection rates of small adenomas and a center's ADR ($P < .001$), but not for large or advanced adenomas. In the high detector group, 6.2% of patients screened were referred to colonoscopy versus 4.5% in the intermediate group and 4.5% in the low group. About half of colonoscopies were conducted by the same endoscopist who performed FS.

During follow-up, the distal CRC incidence was 1.5% in the high ADR group, 1.4% in the intermediate group, and 1.7% in the low group, and mortality rates were 0.4%, 0.4%, and 0.5%, respectively.

Compared with unscreened controls, risk of distal CRC was lowest among individuals who underwent screening in the high ADR group (hazard ratio, 0.34; 95% confidence interval, 0.27-0.42), followed by the intermediate group (HR, 0.46; 95% CI, 0.36-0.59), and the low ADR group (HR, 0.55; 95% CI, 0.44-0.68; $P < .05$ for all).

Compared with unscreened controls, CRC mortality was lower among individuals who underwent screening in the high ADR group (HR, 0.22; 95% CI, 0.13-0.37), followed by the intermediate group (HR, 0.30; 95% CI, 0.17-0.55), and the low ADR group (HR, 0.54; 95% CI, 0.34-0.86; $P < .05$ for between group differences).

All-site CRC incidence followed similar trends, with the lowest risks in the high ADR group (HR, 0.58; 95% CI, 0.50-0.67), followed by intermediate ADR (HR, 0.65; 95% CI, 0.55-0.77) and low ADR groups (HR, 0.72; 95% CI, 0.61-0.85; between-group differences not statistically significant).

All-site CRC mortality was lowest in the high ADR group (HR, 0.52; 95% CI, 0.39-0.69), followed by the intermediate group (HR, 0.53; 95% CI, 0.38-0.73), and the low ADR group (HR, 0.68; 95% CI, 0.51-0.92; between-group differences not statistically significant).

The number needed to screen (NNS) to prevent one CRC diagnosis was 78 in the high ADR group (95% CI, 61-106), 103 in the intermediate group (95% CI, 74-171), and 125 in the low ADR group (95% CI, 82-256). The NNS to prevent one CRC death was 226 (95% CI, 159-387), 247 (95% CI, 165-490), and 349 (95% CI, 192-1,904), respectively.

However, the researchers also pointed out that efforts to increase ADR could result in more complications, such as perforations or gastrointestinal bleeding, as well as more frequent diagnosis and recommended surveillance for diminutive adenomas.

The study is limited by the fact that endoscopists were either gastroenterologists or surgeons and the study population was made up of individuals who desired screening.

The UK Flexible Sigmoidoscopy Screening Trial was funded by the UK Medical Research Council and the National Institute for Health Research. The authors disclosed no conflicts of interest. ■

A denoma detection rate (ADR) is an important quality indicator for colonoscopy. A higher ADR is associated with a lower risk of postcolonoscopy colorectal cancer (CRC). Flexible sigmoidoscopy (FS) is an evidence-based CRC screening modality, supported by multiple randomized trials reporting long-term reduction in CRC incidence and mortality. However, the impact of ADR of endoscopist performing FS on long-term outcomes is not known.


Dr. Shaukat

In this post hoc analysis from the UK Flexible Sigmoidoscopy Screening Trial the authors stratified the 13 endoscopy centers performing screening FS on 40,085 average-risk individuals aged between 55 and 64 years by their ADR into high, intermediate, and low with ADRs of 15%, 12%, and 9%, respectively, and compared the relative reduction in CRC incidence and mortality with 113,195 controls over a median of 17 years. The authors reported greater reduction in both CRC incidence and mortality for CRC between high and low detectors (relative reduction of 42% versus 28% for CRC incidence and 48% versus 32% for CRC mortality, respectively). Differences by ADR for distal CRC were more pronounced between high and low ADR centers (66% versus 45% for CRC incidence and 78% versus 46% for CRC mortality respectively); however, the test for interaction was not statistically significant, suggesting the three ADR groups cannot be differentiated from each other for the outcomes.

While FS is rarely used for screening in the United States, and U.K. guidelines also recently moved away from FS, the study illustrates that quality of FS is important, and that ADR can be a valid quality indicator for flexible sigmoidoscopy.

Aasma Shaukat, MD MPH AGAF, is Robert M. and Mary H. Glickman Professor of Medicine and Population Health and director of GI outcomes research at New York University. She reported having no relevant conflicts of interest.

Human CRP protects against acetaminophen-induced acute liver injury in mice

BY BRANDON MAY
MDedge News

While often linked to deleterious outcomes in certain disease states, the hepatocyte-produced inflammatory marker C-reactive protein (CRP) may be a checkpoint that protects against acetaminophen-induced acute liver injury, according to research findings.

Based on the study findings, researchers believe long-term suppression of CRP function or expression may increase an individual's susceptibility to acetaminophen-induced liver injury (AILI). In contrast, CRP "could be exploited as a promising therapeutic approach to treat hepatotoxicity caused by drug overdose" wrote study authors Hai-Yun Li, MD, of the Xi'an Jiaotong University in Shaanxi, China, and colleagues in Cellular and Molecular Gastroenterology and Hepatology (2021. doi: 10.1016/j.jcmgh.2021.09.004).

According to Dr. Li and colleagues, a major cause of acute liver failure is AILI, but despite this risk, very few treatment options for this condition exist. The only approved treatment for this complication is N-acetyl cysteine.

Although CRP represents a marker for inflammation following tissue injury, a study from 2020 (Front Immunol. 2020. doi: 10.3389/fimmu.2020.01812) and one from 2018 (Front Immunol. 2018 Apr;9:754) suggest the protein regulates complement activation and may modulate responses of immune cells. The authors of the current study noted that few studies have explored what roles complement activation and modulated immune cell responses via CRP play in AILI.

To further elucidate the role of CRP in this setting, Dr. Li and researchers assessed the mechanisms of CRP action both in vitro as well as in CRP mice with Fcy receptor 2B knockout. The researchers suggested CRP may modulate immune cell responses via these receptors. Additionally, the investigators assessed CRP action in mice with C3 knockout, given previous studies suggesting C3 knockout may alleviate acetaminophen-induced liver injury in mice (Pharmacol Exp Ther. 2012;341:377-85). The researchers also investigated hepatic expression of CRP mutants that were defective in complement interaction. Finally, the researchers sought to understand the therapeutic potential of the inflammatory marker by performing intraperitoneal administration of human CRP at 2 or 6 hours after induction of acetaminophen-induced acute liver injury in wild-type mice.

N-acetylcysteine is effective only during the early phases of the AILI and loses effectiveness at 6 hours following injury. In contrast, human CRP in this study was still highly effective at this time point.

Injection of 300 mg/kg acetaminophen over 24 hours led to overt liver injury in wild-type mice, which was characterized by increased levels of circulating alanine transaminase and aspartate transaminase as well as massive necrosis of hepatocytes. The researchers noted that these manifestations were exacerbated significantly in the CRP knockout mice.

The intravenous administration of human CRP in the mice with the drug-induced liver injury rescued defects caused by mouse CRP knockout. Additionally, human CRP administration alleviated acetaminophen-induced acute liver injury in the wild-type mice. The researchers wrote that these findings demonstrate that endogenous and human CRP "are both protective," at least in mouse models of AILI.

In a second experiment, the researchers examined the mechanisms involved in CRP protection in early phases of drug-induced liver injury. Based on the experiment, the researchers found that the knockout of an inhibitory Fcy receptor mediating the anti-inflammatory activities of CRP demonstrated only "marginal effects" on the protection of the protein in AILI. Overall, the investigators suggested that the inflammatory marker does not likely act through the cellular Fcy receptor 2B to inhibit early phases of acetaminophen-induced hepatocyte injury. Rather, the investigators explained that CRP may act through factor H, which is recruited by CRP in regulating complement activation, to inhibit overactivation of complement on injured hepatocytes. Ultimately, the researchers explained, this results in suppression of the late phase amplification of inflammation that is mediated by neutrophils' C3a-dependent actions.

Finally, the researchers found that intraperitoneal administration of human CRP at 2.5 mg/kg in wild-type mice at 2 hours following induction of AILI led to "markedly reduced liver injury," with an efficacy that was similar to that of 500 mg/kg N-acetylcysteine, the only available treatment approved for AILI.

The researchers additionally noted that N-acetylcysteine is effective only during the early phases of the AILI and loses effectiveness at 6 hours following injury. In contrast, human CRP in this study was still highly effective at this time point. "Given that people can tolerate high levels of circulating CRP, the administration of this protein might be a promising option to treat [acetaminophen-induced liver injury] with minimal side effects," the researchers wrote.

The study was funded by the National Natural Science Foundation of China. The researchers reported no conflicts of interest with any pharmaceutical companies. ■

Acetaminophen is one of the most widely used pain relievers in the world. Acetaminophen use is considered safe at therapeutic doses; however, it is a dose-dependent hepatotoxin, and acetaminophen overdose is one of the leading causes of acute liver failure (ALF) in industrialized countries. Despite intensive efforts, the mechanisms involved in acetaminophen hepatotoxicity are not fully understood, which has hampered the availability of effective therapy for acetaminophen hepatotoxicity.


Dr. Fernandez-Checa

In Cellular and Molecular Gastroenterology and Hepatology, Li et al. uncovered a crucial role of C-reactive protein in acetaminophen-mediated ALF. Despite its well recognized role as an acute-phase protein in inflammation, CRP also regulates complement activation and hence the modulation of immune cell responses and the generation of anaphylotoxins via specific receptors. With use of models of genetic deletion of CRP in rats and mice, Li et al. demonstrate a protective role for CRP in acetaminophen-induced ALF by regulating the late phase of acetaminophen-induced liver failure via complement overactivation through antagonism of C3aR that prevented neutrophil recruitment.

From a clinically relevant perspective, the protective effect of CRP was more effective than the currently used therapeutic approach of giving N-acetylcysteine (NAC) to patients after acetaminophen hepatotoxicity. The superiority of CRP vs. NAC is related to the limited period for NAC administration after acetaminophen overdose, while the administration of CRP was effective even when given several hours after acetaminophen dosage, consistent with its ability to target the late phase of events involved in acetaminophen hepatotoxicity. Therefore, these findings identify CRP as a promising approach for acetaminophen hepatotoxicity with significant therapeutic advantage, compared with NAC treatment, which may change the paradigm of management of acetaminophen-induced liver failure.

Jose C. Fernandez-Checa, PhD, is a professor at the Spanish National Research Council at the Institute of Biomedical Research of Barcelona, investigator of the Institute of Biomedical Research August Pi i Sunyer, group leader of the Center for Biomedical Network Research on Hepatic and Digestive Diseases, and visiting professor at the department of medicine University of Southern California, Los Angeles. He has no relevant conflicts of interest.

See Gastroenterology's curated 'Equity in GI' journal collection

Gastroenterology is proud to announce the release of a special collection of articles focused on the intersection of diversity, equity, and inclusion (DEI) within gastroenterology and hepatology.

This curated collection, under the guidance of the journal's new DEI section editor Chyke Doubeni, MBBS, MPH, includes original research, reviews, commentaries, and editorials on matters of health disparities, socioeconomic determinants of health outcomes, and population-based studies on disease incidence among races and ethnicities, among others. New articles are added to the collection as they are published.

View the special collection on Gastroenterology's website, which is designed to help you quickly and easily look over the latest DEI articles and content of interest. Recent articles include the following:

- "How to incorporate health equity training into GI/hepatology fellowships," by Jannel Lee-Allen, MD, and Brijen J. Shah, MD.
- "Disparities in preventable mortality from colorectal cancer: Are they the result of structural racism?" by Chyke A. Doubeni, MBBS, MPH; Kevin Selby, MD; and Theodore R. Levin, MD.
- "COVID-19 pediatric patients: GI symptoms, presentations and disparities by race/ethnicity in a large, multicenter U.S. study," by Yusuf Ashktorab, MD; Anas Brim, MD; Antonio Pizuorno, MD; Vijay Gayam, MD; Sahar Nikdel, MD; and Hassan Brim, PhD.

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Closer post-ESD surveillance for early GI neoplasia warranted

The new AGA Clinical Practice Update on Surveillance After Pathologically Curative Endoscopic Submucosal Dissection of Early Gastrointestinal Neoplasia in the United States: Commentary offers advice regarding surveillance intervals using endoscopy and other relevant modalities after endoscopic removal of dysplastic lesions and early GI cancers with endoscopic submucosal dissection (ESD) which were deemed pathologically curative.

Main takeaway: Patients with malignant lesions removed by curative ESD possess a higher risk of lymph node metastasis and should be surveilled more closely than those with resection dysplasia not associated with lymphatic spread.

Dean Mitchell/Thinkstock

Gut Microbiota for Health World Summit 2022

Registration is now open for the Gut Microbiota for Health (GMFH) World Summit 2022, taking place March 12-13 in Washington, D.C., and virtually.

Organized by AGA and the European Society of Neurogastroenterology and Motility (ESNM), the GMFH World Summit is the preeminent international meeting on the gut microbiome for clinicians, dietitians, and researchers.

Now in its 10th year, the program for this year's conference will focus on "The Gut Microbiome in Precision Nutrition and Medicine." Join us to gain a deeper understanding of the role of the gut microbiome in precision medicine and discover personalized approaches to modulating the gut microbiome that may promote health and improve patient outcomes for a variety of disorders and diseases.

DDSEP 9 Digestive Diseases Self-Education Program

Quick quiz

Q1. A 74-year-old female with a history of recurrent deep vein thrombosis on therapeutic warfarin presents to the emergency department with 1 hour of large volume bright red blood per rectum. Vital signs are as follows: heart rate, 110 bpm; blood pressure, 72/48 mm Hg. Examination reveals a pale, confused female in no acute distress, tachycardia, and a soft nontender abdomen without distension and no stigmata of liver disease. Lab results reveal international normalized ratio, 2.0; hemoglobin, 6.4 g/dL; and platelet count, 180,000/uL. Intravenous access is established, and crystalloid resuscitation is initiated. An urgent upper endoscopy reveals no blood or etiology for massive hematochezia. Despite resuscitation and transfusion of packed red blood cells, the patient continues to have massive hematochezia and remains confused and hypotensive requiring vasopressors and ICU support.

What is the next best step in management of this patient?

A. Emergent reversal of coagulopathy.
B. Rapid bowel prep and urgent colonoscopy.
C. Emergent unprepped colonoscopy.
D. Nuclear tagged RBC scan.
E. Emergent angiography.

Q2. A 22-year-old man with a history of extensive ulcerative colitis diagnosed 3 years ago presents for evaluation. He is currently in clinical remission, maintained on oral mesalamine 2.4 g/day in divided doses. He was noted to have persistent elevation of serum alkaline phosphatase on blood samples drawn 3 months apart. Magnetic resonance cholangiopancreatography (MRCP) revealed alternating narrowed and dilated segments of the intrahepatic and extrahepatic biliary ducts consistent with primary sclerosing cholangitis (PSC).

Which of the following is recommended at this time?

A. Repeat MRCP in 6 months for screening.
B. He should undergo surveillance colonoscopy now and annually thereafter.
C. First surveillance colonoscopy is recommended 5 years from now, and annually thereafter.
D. High-dose ursodeoxycholic acid (UDCA) should be started.

The answers are on page 23

U.S. Multi-Society Task Force Clinical Practice Guideline

Updates on ages for colorectal cancer screening

BY WILL PASS
MDedge News

The U.S. Multi-Society Task Force on Colorectal Cancer (CRC) has lowered the recommended age to start CRC screening from 50 to 45 years of age for all average-risk individuals.

Although no studies have directly demonstrated the result of lowering the age of screening, lead author Swati G. Patel, MD, of University of Colorado Anschutz Medical Center, Aurora, and colleagues suggested that the increasing incidence of advanced CRC among younger individuals, coupled with the net benefit of screening, warrants a lower age threshold.

"Recent data ... show that CRC incidence rates in individuals ages 50 to 64 have increased by 1% annually between 2011 and 2016," the authors wrote in Gastroenterology (2021 Nov 15. doi: 10.1053/j.gastro.2021.10.007). "Similarly, CRC incidence and mortality rates in persons under age 50, termed early-age onset CRC (EAO-CRC), are also increasing."

The task force of nine experts, representing the American Gastroenterological Association, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy, conducted a literature review and generated recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria. In addition to recommending a lower age for initial screening, Dr. Patel and colleagues provided guidance for cessation of screening among older individuals.


Dr. Patel

The increasing incidence of advanced CRC among younger individuals, coupled with the net benefit of screening, warrant a lower age threshold.

Guidance for screening initiation

According to the authors, the present risk of CRC among younger individuals mirrors the historical risk for older individuals before screening was prevalent.

"The current CRC incidence rates in individuals ages 45 to 49 are similar to the incidence rates observed in 50-year-olds in 1992, before widespread CRC screening was performed," they wrote.

Elevated rates among younger people have been disproportionately driven by rectal cancer, according to the authors. From 2006 to 2015, incidence of rectal cancer among Americans under 50 increased 1.7% per year, compared with 0.7% per year for colon cancer, based on data from the North American Association of Central Cancer Registries (J Natl Cancer Inst. 2019 Oct 1;111[10]:1104-6).

Associated mortality rates also increased, the authors noted. From 1999 to 2019, mortality from colon cancer among people 45-49 years increased from 6.4 to 6.6 deaths per 100,000 individuals, while deaths from rectal cancer increased from 1.3 to 1.7 per 100,000, according to the CDC. Concurrently, CRC-associated mortality rates among older individuals generally declined.

While these findings suggest a growing disease burden among the under-50-year age group, controlled data demonstrating the effects of earlier screening are lacking, Dr. Patel and colleagues noted. Still, they predicted that expanded screening would generate a net benefit.

"Although there are no CRC screening safety data for average-age-risk individuals [younger than] 50, there are ample data that colonoscopy for other indications (screening based on family history, symptom evaluation, etc.) is safer when comparing younger versus older individuals," they wrote.

Supporting this claim, the authors cited three independently generated microsimulation models from the Agency for Healthcare Research and Quality that "showed a favorable balance of life-years gained compared with adverse events," given 100% compliance.

Guidance for screening cessation

Like the situation with younger individuals, minimal data are available to determine the best time for screening cessation, according to the task force.

"There are no randomized or observational studies after 2017 that enrolled individuals over age 75 to inform the appropriate time to stop CRC screening," the authors wrote. "In our search of 37 relevant articles, only one presented primary data for when to stop screening."

This one available study (Clin Gastroenterol Hepatol. 2021 Mar;19[3]:547-55) showed that some individuals older than 74 do in fact gain benefit from screening,

"For example," Dr. Patel and colleagues wrote, "women without a history of screening and no comorbidities benefitted from annual fecal immunochemical test (FIT) screening until age 90, whereas unscreened men with or without comorbidities benefited from annual FIT screening until age 88. Conversely, screening was not beneficial beyond age 66 in men or women with severe comorbidities."

The task force therefore recommended personalized screening for individuals 76-85 years of age "based on the balance of benefits and harms and individual patient clinical factors and preferences."

Screening for individuals 86 years and older, according to the task force, is unnecessary.

The authors disclosed relationships with Olympus America, Bayer Pharmaceuticals, Janssen Pharmaceuticals, and others. ■

Private insurers must cover follow-up colonoscopies

BY HEIDI SPLETE
MDedge News

PhotoAlto/Frederic Cirou

Private insurers are now required to cover the cost of follow-up colonoscopies after a positive stool-based test, according to updated guidance from the Biden administration cited in a press release from the American Gastroenterological Association.

"Now patients can choose the best colorectal cancer screening test for them without fear of a surprise bill. Patients have full coverage of the full screening continuum – from an initial stool or endoscopic test to a follow-up colonoscopy. Now that the financial barriers have been eliminated, we can focus on increasing screening so we can prevent cancer deaths," says John Inadomi, MD, president of the AGA, in the AGA press release.

The updated guidance, issued on Jan. 10, 2022, "will prevent patients from receiving surprise bills for a colonoscopy when they receive a positive result from a stool-based test," according to the AGA press release.

In 2016, the U.S. Preventive Services Task Force recommended colorectal cancer screening for all adults starting at age 50 years and continuing to age 75 years, with an "A" rating. Because the Affordable Care Act (ACA) mandated coverage for preventive screenings without cost-sharing that receive an "A" or "B" grade from the USPSTF, previous statements have confirmed that cost sharing may not be imposed on patients for screening in accordance with the USPSTF recommendation, which included specialist consultation prior to the procedure, bowel prep medications, anesthesia services in conjunction with a preventive colonoscopy, polyp removal performed during the screening procedure, and any pathology exam on a polyp biopsy performed as part of the screening.

"Patients have full coverage of the full screening continuum – from an initial stool or endoscopic test to a follow-up colonoscopy."

By adding colonoscopies following positive stool tests to that list, the updated guidance means that all aspects of the screening procedure are now covered without cost sharing.

In May 2021, an update to the USPSTF recommendations called for a follow-up colonoscopy in the wake of a positive test: "Positive results on stool-based screening tests require follow-up with colonoscopy for the screening benefits to be achieved." The 2021 update also extended the screening recommendation to adults aged 45-49 years with a "B" rating.

Private insurers must now pay for follow-up colonoscopy as needed in addition to the initial noninvasive screening, according to the guidance.

The updated guidance is presented as part of a series of frequently asked questions documents regarding implementation of the Families First Coronavirus Response Act, the Coronavirus Aid, Relief, and Economic Security Act, and the Affordable Care Act. The colonoscopy guidance falls under the heading of "Coverage of Preventive Services," which includes evidence-based recommendations given an A or B rating by the USPSTF.

Coverage without cost sharing must begin on or after May 31, 2022, which is 1 year after the date of the latest recommendations, according to the FAQ.

Representatives of multiple organizations, including the AGA, American Cancer Society, American Cancer Society Cancer Action Network, and Fight CRC collaborated to promote the additional coverage. "We applaud the administration for supporting coverage of the full colorectal cancer screening continuum, which will improve access to life-saving screening," the collaborators said in the press release.

Colorectal cancer remains the second leading cancer killer in the United States, but only two-thirds of eligible individuals were screened in 2018, according to the AGA, and screening challenges were exacerbated by the arrival of the COVID-19 pandemic. ■

The management of inflammatory bowel disease in pregnancy

BY RISHIKA CHUGH, MD, AND UMA MAHADEVAN, MD

Inflammatory bowel disease (IBD) incidence is rising globally.[1-3] In the United States, we have seen a 123% increase in prevalence of IBD among adults and a 133% increase among children from 2007 to 2016, with an annual percentage change of 9.9%.[1] The rise of IBD in young people, and the overall higher prevalence in women compared with men, makes pregnancy and IBD a topic of increasing importance for gastroenterologists.[1] Here, we will discuss management and expectations in women with IBD before conception, during pregnancy, and post partum.

Preconception

Disease activity

Achieving both clinical and endoscopic remission of disease prior to conception is the key to ensuring the best maternal and fetal outcomes. Patients with IBD who conceive while in remission remain in remission 80% of the time.[4,5] On the other hand, those who conceive while their disease is active may continue to have active or worsening disease in nearly 70% of cases.[4] Active disease has been associated with an increased incidence of preterm birth, low birth weight, and small-for-gestational-age birth.[6-8] Active disease can also exacerbate malnutrition and result in poor maternal weight gain, which is associated with intrauterine growth restriction.[7,9] Pregnancy outcomes in patients with IBD and quiescent disease are similar to those in the general population.[10,11]

Health care maintenance

Optimizing maternal health prior to conception is critical. Alcohol, tobacco, recreational drugs, and marijuana should all be avoided. Opioids should be tapered off prior to conception, as continued use may result in neonatal opioid withdrawal syndrome and long-term neurodevelopmental consequences.[12,13] In addition, aiming for a healthy body mass index between 18 and 25 months prior to conception allows for better overall pregnancy outcomes.[13] Appropriate cancer screening includes colon cancer screening in those with more than 8 years of colitis, regular pap smear for cervical cancer, and annual total body skin cancer examinations for patients on thiopurines and biologic therapies.[14]

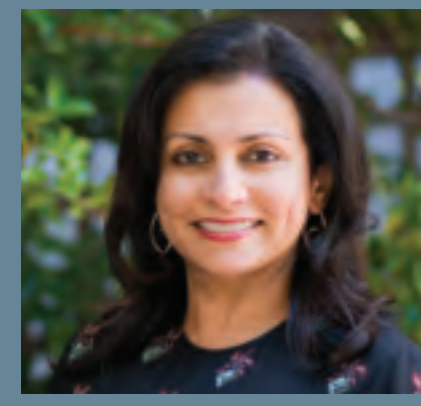
Nutrition

Folic acid supplementation with at least 400 mcg daily is necessary for all women planning pregnancy. Patients with small-bowel involvement or history of small-bowel resection should have a folate intake of a minimum of 2 g per day. Adequate vitamin D levels (at least 20 ng/mL) are recommended in all women with IBD. Those with malabsorption should be screened for deficiencies in vitamin B_{12}, folate, and iron.[13] These nutritional markers should be evaluated prepregnancy, during the first trimester, and thereafter as needed.[15-18]

Preconception counseling

Steroid-free remission for at least 3 months prior to conception is recommended and is associated with reduced risk of flare during pregnancy.[16,19] IBD medications needed to control disease activity are generally safe preconception and during pregnancy, with some exception.

Misconceptions regarding heritability of IBD have sometimes discouraged men and women from having children. While genetics may increase susceptibility, environmental and other factors are involved as well. The concordance rates for monozygotic twins range from 33.3% to 58.3% for Crohn's disease and 13.4% to 27.9% for ulcerative colitis (UC).[20] The risk of a child developing IBD is higher in those who have multiple relatives with IBD and whose parents had IBD at the time of conception.[21] While genetic testing for IBD loci is available, it is not commonly performed at this time as many genes are involved.[22]



Dr. Chugh is an advanced inflammatory bowel disease fellow in the division of gastroenterology at the University of California San Francisco. **Dr. Mahadevan** is professor of medicine and director at the Center for Colitis and Crohn's Disease in the division of gastroenterology at the University of California San Francisco. Dr. Mahadevan has potential conflicts related to AbbVie, Janssen, BMS, Takeda, Pfizer, Lilly, Gilead, Arena, and Prometheus Biosciences.

Pregnancy

Coordinated care

A complete team of specialists with coordinated care among all providers is needed for optimal maternal and fetal outcomes.[23,24] A gastroenterologist, ideally an IBD specialist, should follow the patient throughout pregnancy, seeing the patient at least once during the first or second trimester and as needed during pregnancy.[16] A high-risk obstetrician or maternal fetal medicine specialist should be involved early in pregnancy, as well. Open communication among all disciplines ensures that a common message is conveyed to the patient.[16,24] A nutritionist, mental health provider, and lactation specialist knowledgeable about IBD drugs may be of assistance, as well.[16]

Disease activity

While women with IBD are at increased risk of spontaneous abortion, preterm birth, and labor complications, this risk is mitigated by controlling disease activity.[25] The risk of preterm birth, small-for-gestational-age birth, and delivery via C-section is much higher in women with moderate to high disease activity, compared with those with low disease activity.[26] The presence of active perianal disease mandates C-section over vaginal delivery. Fourth-degree lacerations following vaginal delivery are most common among those patients with perianal disease.[26,27] Still births were shown to be increased only in those with active IBD when compared with non-IBD comparators and inactive IBD.[11;28-31]

Noninvasive methods for disease

The management of inflammatory bowel disease (IBD) in pregnancy can be particularly difficult to navigate with the litany of therapeutic options and their varying safety profiles. Even so, understanding the appropriate use of pharmacotherapy is of critical importance given the high proportion of young women with IBD who are planning to conceive, pregnant, or in the postpartum period.

The In Focus article for February, which is brought to you by The New Gastroenterologist, nicely elucidates the complex management issues surrounding IBD in pregnancy. Dr. Rishika Chugh and Dr. Uma Mahadevan (UCSF) provide a comprehensive multifaceted approach, first discussing the importance of health care maintenance and disease control in the preconception stage, then focusing on safety considerations and how to choose the right therapeutic regimen for pregnant patients.

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

monitoring are preferred in pregnancy, but serum markers such as erythrocyte sedimentation rate and C-reactive protein may not be reliable in the pregnant patient (see Figure).[32] Fecal calprotectin does rise in correlation with disease activity, but exact thresholds have not been validated in pregnancy.[33,34]

An unsedated, unprepped flexible sigmoidoscopy can be safely performed throughout pregnancy.[35] When there is a strong indication, a complete colonoscopy can be performed in the pregnant patient as well.[36] Current American Society for Gastrointestinal Endoscopy guidelines suggest placing the patient in the left lateral tilt position to avoid decreased maternal and placental perfusion via compression of the aorta or inferior vena cava and performing endoscopy during the second trimester, although trimester specific timing is not always feasible by indication.[37]

Medication use and safety

IBD medications are a priority topic of concern among pregnant patients or those considering conception.[38] Comprehensive data from the PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) registry has shown that most IBD drugs do not result in adverse pregnancy outcomes and should be continued.[39] The use of biologics and thiopurines, either in combination or alone, is not related to an increased risk of congenital malformations, spontaneous abortion, preterm birth, low birth weight, or infections during the child's first year of life.[7,39] Developmental milestones also remain unaffected.[39] Here, we will discuss safety considerations during pregnancy (see Table).

5-aminosalycylic acid. 5-aminosalicylic acid (5-ASA) agents are generally low risk during pregnancy and should be continued.[40,41] Sulfasalazine does interfere with folate metabolism, but by increasing folic acid supplementation to 2 g per day, sulfasalazine can be continued throughout pregnancy, as well.[42]

Corticosteroids. Intrapartum corticosteroid use is associated with an increased risk of gestational diabetes and adrenal insufficiency when used long term.[43-45] Short-term use may, however, be necessary to control an acute flare. The lowest dose for the shortest duration possible is recommended. Because of its high first-pass metabolism, budesonide is considered low risk in pregnancy.

Methotrexate. Methotrexate needs to be stopped at least 3 months prior to conception and should be avoided throughout pregnancy. Use during pregnancy can result in spontaneous abortions, as well as embryotoxicity.[46]

Thiopurines (6-mercaptopurine and azathioprine). Patients who are taking thiopurines prior to conception to maintain remission can continue to do so. Data on thiopurines from the PIANO registry have shown no increase in spontaneous abortions, congenital malformations, low birth weight, preterm birth, rates of infection in the child, or developmental delay.[47-51]

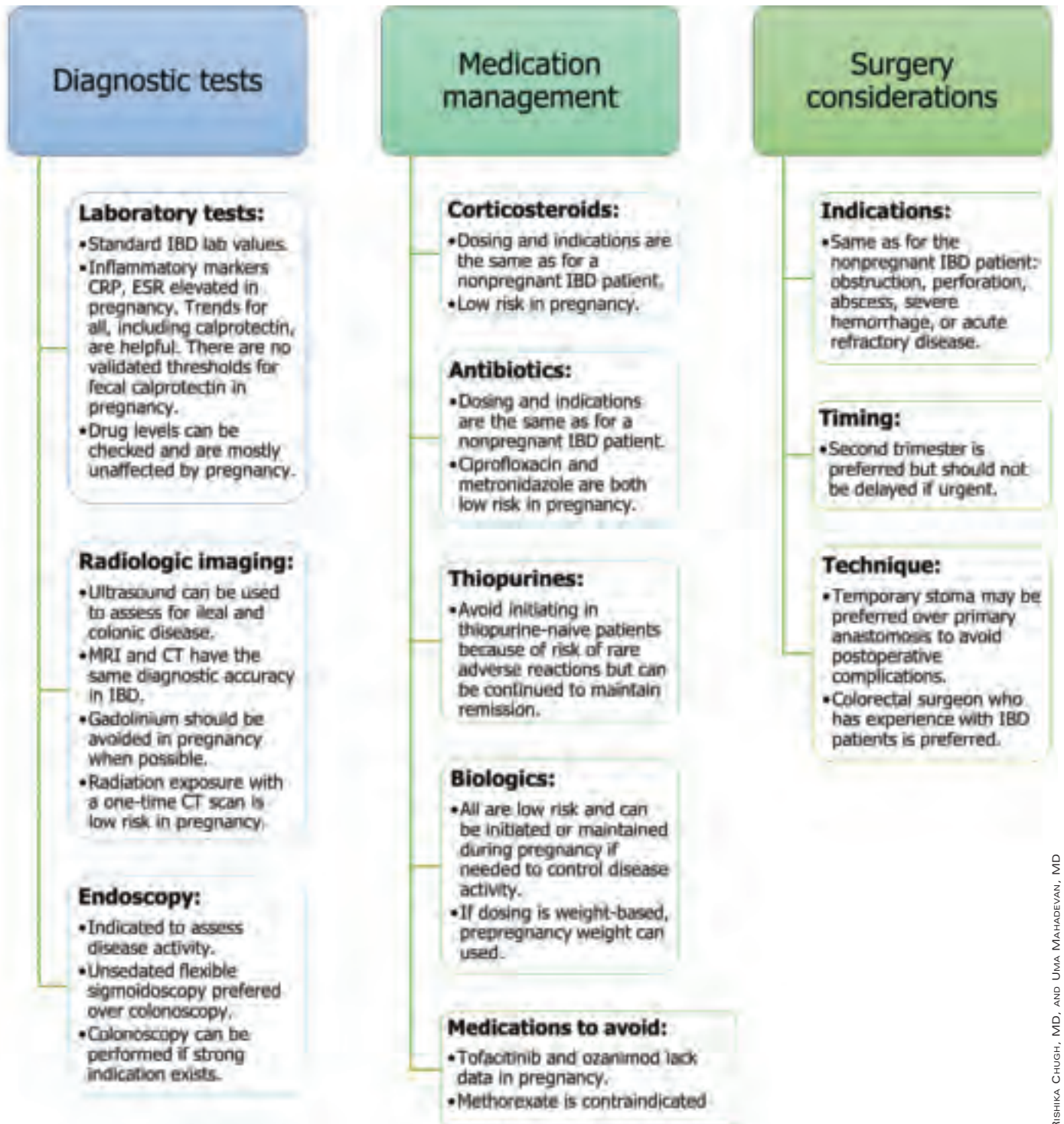
Calcineurin inhibitors (cyclosporine and tacrolimus). Calcineurin inhibitors are reserved for the management of acute severe UC. Safety data on calcineurin inhibitors are conflicting, and there is not enough information at this time to identify risk during pregnancy. Cyclosporine can be used for salvage therapy if absolutely needed, and there are case reports of its successful use during pregnancy.[16,52]

Biologic therapies. With the exception of certolizumab, all of the currently used biologics are actively transported across the placenta.[39,53,54] Intrapartum use of biologic therapies does not worsen pregnancy or neonatal outcomes, including the risk for intensive care unit admission, infections, and developmental milestones.[39,47]

While drug concentrations may vary slightly during pregnancy, these changes are not substantial enough to warrant more frequent

Continued on following page

Figure. Management of inflammatory bowel disease flare during pregnancy



IBD: inflammatory bowel disease, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MRI: magnetic resonance imaging, CT: computed tomography

Rishika Chugh, MD, and Uma Mahadevan, MD

Continued from previous page

monitoring or dose adjustments, and prepregnancy weight should be used for dosing.[55,56]

Anti–tumor necrosis factor agents used in IBD include infliximab, adalimumab, certolizumab, and golimumab.[57] All are low risk for pregnant patients and their offspring. Dosage timings can be adjusted, but not stopped, to minimize exposure to the child; however, it should not be adjusted for certolizumab pegol because of its lack of placental transfer.[58,59]

Natalizumab and vedolizumab are integrin receptor antagonists and are also low risk in pregnancy.[39,57,60-62]

Ustekinumab, an interleukin-12/23 antagonist, can be found in infant serum and cord blood, as well. Health outcomes are similar in the exposed mother and child, however, compared with those of the general population.[39,63-64]

Small-molecule drugs. Unlike monoclonal antibodies, which do not cross the placenta in large amounts until early in the second trimester, small molecules can cross in the first trimester during the critical period of organogenesis.

The two small-molecule agents currently approved for use in UC are tofacitinib, a Janus kinase inhibitor, and ozanimod, a sphingosine-1-phosphate receptor agonist.[65,66] Further data are still needed to make recommendations on the use of tofacitinib and ozanimod in pregnancy. At this time, we recommend weighing the risks (unknown risk to human pregnancy) vs. benefits (controlled disease activity with clear risk of harm to mother and baby from flare) in the individual patient before counseling on use in pregnancy.

Delivery

Mode of delivery

The mode of delivery should be determined by the obstetrician. C-section is recommended for patients with active perianal disease or, in some cases, a history of ileal pouch anal anastomosis (IPAA).[67,68] Vaginal delivery in the setting of perianal disease has been shown to increase the risk of fourth-degree laceration and anal sphincter dysfunction in the future.[26-27] Anorectal motility may be impacted by IPAA construction and vaginal delivery independently of each other. It is therefore suggested that vaginal delivery be avoided in patients with a history of IPAA to avoid compounding the risk. Some studies do not show clear harm from vaginal delivery in the setting of IPAA, however, and informed decision making among all stakeholders should be had.[27,69-70]

Anticoagulation

The incidence of venous thromboembolism (VTE) is elevated in patients with IBD during pregnancy, and up to 12 weeks postpartum, compared with pregnant patients without IBD.[71-72] VTE for prophylaxis is indicated in the pregnant patient while hospitalized and potentially thereafter depending on the patient's risk factors, which may include obesity, prior personal history of VTE, heart failure, and prolonged immobility. Unfractionated heparin, low–molecular weight heparin, and warfarin are safe for breastfeeding women.[16,73]

Postpartum care of mother

There is a risk of postpartum flare, occurring in about one-third of patients in the first 6 months post partum.[74,75] De-escalating therapy during delivery or immediately postpartum is a predictor of a postpartum flare.[75] If no infection is present and the timing interval is appropriate, biologic therapies should be continued and can be resumed 24 hours after a vaginal delivery and 48 hours after a C-section.[16,76]

NSAIDs and opioids can be used for pain relief but should be avoided in the long-term to prevent flares (NSAIDs) and infant sedation (associated with opioids) when used while breastfeeding.[77] The LactMed database is an excellent resource for clarification on risk of medication use while breastfeeding.[78]

In particular, contraception should be addressed post partum. Exogenous estrogen use increases the risk of VTE, which is already increased in IBD; non-estrogen containing, long-acting reversible contraception is preferred.[79,80] Progestin-only implants or intrauterine devices may be used first line. The efficacy of oral contraceptives is theoretically reduced in those with rapid bowel transit, active small-bowel inflammation, and prior small-bowel resection, so adding another form of contraception is recommended.[16,81]

Postdelivery care of baby

Breastfeeding

Guidelines regarding medication use during breastfeeding are similar to those in pregnancy (see Table). Breastfeeding on biologics and thiopurines can continue without interruption. Thiopurine concentrations in breast milk are

Table. IBD medications and their impact on pregnancy and breastfeeding

Medications	Pregnancy safety	Breastfeeding considerations
5-aminosalicylic acid	↓ Low risk. Sulfasalazine okay with increased dose of folic acid (2 g/day).	5-aminosalicylic acid agents are low risk. Risk of hemolysis with sulfasalazine, especially if child has glucose-6 phosphate dehydrogenase deficiency.
Corticosteroids	↓ Low risk. Gestational diabetes and adrenal insufficiency with long-term use.	Breast milk concentrations are low. IV steroids may temporarily suppress lactation.
Antibiotics		
Ciprofloxacin	↓ Low risk. Short-term use recommended.	Breast milk concentrations are low.
Metronidazole	↓ Low risk. Short-term use recommended.	Can cause infant diarrhea. Avoid breastfeeding 12-24 hours after dose.
Immunomodulators		
Methotrexate	↑ High risk. Stop 3 months prior to conception.	Avoid while breastfeeding.
Thiopurines		
6-mercaptopurine	↓ Low risk.	Breast milk concentrations are low.
Azathioprine	↓ Low risk.	Breast milk concentrations are low.
Calcineurin inhibitors		
Tacrolimus and cyclosporine	Not enough data. Data come from post-transplant recipients and are conflicting. Potential complications include pre-eclampsia and uncontrolled hypertension in the mother, as well as low birth weight, spontaneous abortion, and preterm birth.[16,44]	Data from National Transplant Pregnancy Registry suggest continued use with close monitoring.
Biologic therapies		
Antitumor necrosis factor	All are monoclonal antibodies and cross the placenta (except certolizumab), but continued use during pregnancy does not result in any adverse outcomes for the mother or offspring.[39;53-54]	
Adalimumab	↓ Low risk.	Breast milk concentrations are low or undetectable.
Infliximab	↓ Low risk.	Breast milk concentrations are low or undetectable.
Golimumab	↓ Low risk.	Breast milk concentrations are low or undetectable.
Certolizumab pegol	↓ Low risk. Does not cross the placenta.	Breast milk concentrations are low or undetectable.
Anti-integrin	Continued use during pregnancy does not result in any adverse outcomes for the mother or offspring.[60-62; 39]	
Natalizumab	↓ Low risk.	Breast milk concentrations are low or undetectable.
Vedolizumab	↓ Low risk.	Breast milk concentrations are low or undetectable.
Anti-interleukin 12/23	As with other biologics, health outcomes are similar in the exposed mother and child, compared with those of the general population.[39;63-64]	
Ustekinumab	↓ Low risk.	Breast milk concentrations are low or undetectable.
Small molecule therapies		
Janus kinase inhibitor		
Tofacitinib	Not enough data. Animal studies demonstrate the possibility of teratogenic effects with supratherapeutic doses. Small human studies have found no harm.[51]	Not enough data. Avoid use during breastfeeding at this time.
Sphingosine-1-phosphate agonist		
Ozanimod	Not enough data. Animal and observational human studies have demonstrated that early pregnancy exposure does not result in adverse effects.[66]	Not enough data. Avoid use during breastfeeding at this time.

Source: Dr. Chugh, Dr. Mahadevan

low or undetectable.[78,82] TNF receptor antagonists, anti-integrin therapies, and ustekinumab are found in low to undetectable levels in breast milk, as well.[78]

On the other hand, the active metabolite of methotrexate is detectable in breast milk and most sources recommend not breastfeeding on methotrexate. At doses used in IBD (15-25 mg per week), some experts have suggested avoiding breastfeeding for 24 hours following a dose.[57,78] It is the practice of this author to recommend not breastfeeding at all on methotrexate.

5-ASA therapies are low risk for breastfeeding, but alternatives to sulfasalazine are preferred. The sulfapyridine metabolite transfers to breast milk and may cause hemolysis in infants born with a glucose-6-phosphate dehydrogenase deficiency.[78]

Infant exposure to biologics and thiopurines has not been shown to result in any developmental delay.

With regards to calcineurin inhibitors, tacrolimus appears in breast milk in low quantities, while cyclosporine levels are variable. Data from the National Transplantation Pregnancy Registry suggest that these medications can be used at the time of breastfeeding with close monitoring.[78]

There are not enough data on small-molecule therapies at this time to support breastfeeding safety, and it is our practice to not recommend breastfeeding in this scenario.

The transfer of steroids to the child via breast milk does occur but at subtherapeutic levels.[16] Budesonide has high first pass metabolism and is low risk during breastfeeding.[83,84] As far as is known, IBD maintenance medications do not suppress lactation. The use of intravenous corticosteroids can, however, temporarily decrease milk production.[16,85]

Vaccines

Vaccination of infants can proceed as indicated by the Center for Disease Control and Prevention guidelines, with one exception. If the child's mother was exposed to any biologic agents (not including certolizumab) during the third trimester, any live vaccines should be withheld in the first 6 months of life. In the United States, this restriction currently applies only to the rotavirus vaccine, which is administered starting at the age of 2 months.[16,86] Notably, inadvertent administration of the rotavirus vaccine in the biologic-exposed child does not appear to result in any adverse effects.[87] Immunity is achieved even if the child is exposed to IBD therapies through breast milk.[88]

Developmental milestones

Infant exposure to biologics and thiopurines has not been shown to result in any developmental delay. The PIANO study measured developmental milestones at 48 months from birth and found no differences when compared with validated population norms.[39] A separate study observing childhood development up to 7 years of age in patients born to mothers with IBD found similar cognitive scores and motor development when compared with those born to mothers without IBD.[89]

Conclusion

Women considering conception should be optimized prior to pregnancy and maintained on appropriate medications throughout pregnancy and lactation to achieve a healthy pregnancy for both mother and baby. To date, biologics and thiopurines are not associated with adverse pregnancy outcomes. More data are needed for small molecules. ■

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

Vedolizumab safety reinforced

CDI *from page 1*

flares, further adding to the physical and psychological burden associated with the condition, according to recent studies (Therap Adv Gastroenterol. 2021 May 30. doi: 10.1177/17562848211020285).

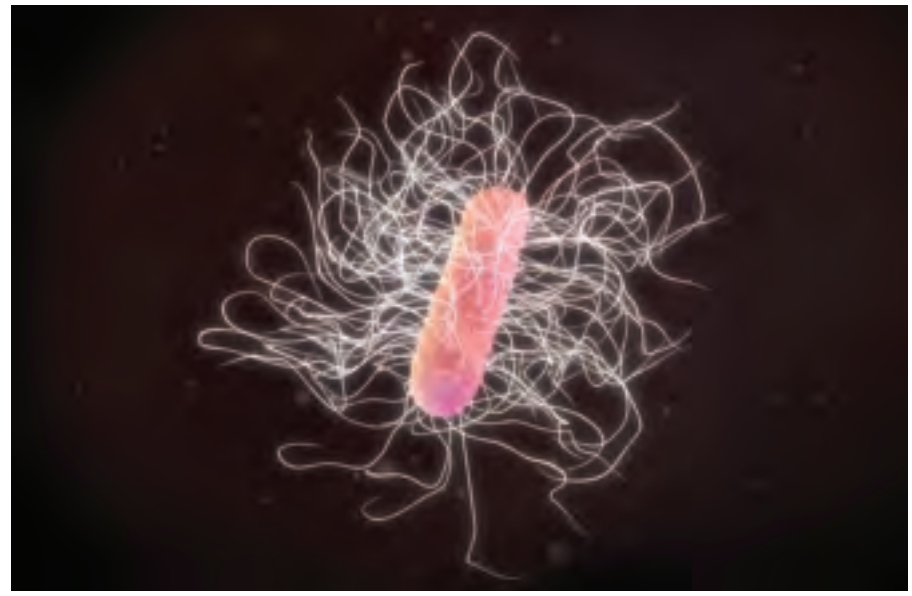
These concerns, however, may not be warranted in patients with UC, according to findings from a retrospective study presented at the annual Advances in Inflammatory Bowel Diseases conference by Rahul Dalal, MD, a gastroenterology fellow at Brigham and Women's Hospital in Boston.

In the study, Dr. Dalal and colleagues retrospectively analyzed electronic medical records of adult patients with UC who initiated infliximab, adalimumab, or vedolizumab between June 2014 and December 2020. Patients in this retrospective cohort were followed until there was a documented occurrence of CDI, colectomy, or biologic discontinuation/switch, or until the last recorded gastroenterology encounter.

The researchers analyzed the time from biologic initiation to first CDI, which was characterized by a positive stool for *C. difficile* toxin or toxigenic *C. difficile* polymerase chain reaction with CDI-specific antibiotic prescriptions. Additionally, the investigators evaluated rates of CDI-related hospitalization, colectomy, or death within a 30-day period of CDI. The primary analysis compared patients with UC who initiated vedolizumab (n = 195) versus anti-TNF therapy (n = 610).

Compared with those treated with anti-TNF agents, patients who initiated vedolizumab were older and less frequently received systemic corticosteroids or had UC-related hospitalization within 12 months prior to starting biologics.

Over 1,436 patient-years' worth of follow-up, the investigators observed 43 CDIs. Patients treated with vedolizumab less frequently had CDI (1.0% vs. 6.7%; *P* =.001) and CDI hospitalization (1.0% vs. 3.8%; *P* =.042), compared with those treated with anti-TNF therapies. The investigators reported no significant differences in the rates of colectomies or deaths or rates of exposure to antibiotics/corticosteroids during the follow-up period or within 30 days prior to CDI onset.



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In the unadjusted Cox model, the researchers reported that vedolizumab featured a lower hazard of CDI, compared with anti-TNF (hazard ratio, 0.17; 95% confidence interval, 0.04-0.71). The multivariable Cox model found no significant difference in hazard of CDI for vedolizumab when compared with anti-TNF therapy (HR, 0.33; 95% CI, 0.05-2.03) or immunomodulator exposure (HR, 1.01; 95% CI, 0.41-2.40). The incidence of CDI prior to biologic initiation was associated with an increased hazard of subsequent CDI (HR, 5.95; 95% CI, 2.93-12.09). In the subgroup of patients who experienced a CDI, approximately 39.5% had CDI before biologic initiation at a median of 227 days preceding the subsequent event.

"Vedolizumab is one of the safest biologics that we have in the clinic," said Jean-Frederic Colombel, MD, who was asked to comment on the study. Dr. Colombel, who wasn't involved in the study, is a gastroenterologist and serves as director of the Feinstein IBD Center at Mount Sinai Hospital and professor of medicine (division of gastroenterology) at the Icahn School of Medicine at Mount Sinai, both in New York. "Findings from this study reinforce the safety profile of vedolizumab" despite the potential concerns regarding gastroenterological infection with the agent, he added.

Recurrence worries

Recurrent CDI is an issue in patients with IBD, many of whom are considered at high risk for initial and recurrent infection. During a session on CDI and recurrence at the AIBD meeting, Sahil Khanna, MBBS, of the Mayo Clinic, explained that there are three different treatment guidelines to manage initial CDI in patients with IBD.

Predominantly, these guidelines also suggest human monoclonal antibody bezlotoxumab could be used for prevention of CDI recurrence in patients at high risk of recurrence, including those who had experienced severe CDI. "One can argue that anyone with IBD who has *C. difficile* can be a severe CDI patient because of the bad outcomes we can see," he explained.

"We do know that IBD is a state of chronic microbial dysbiosis compared to our patients without IBD who get *C. difficile* because of antibiotic exposure, and that's why these patients have a high risk of recurrence, compared with non-IBD patients," said Dr. Khanna. He noted that the bezlotoxumab studies showed numerically lower CDI recurrence rates compared with other treatments in patients with IBD who were initially treated with the monoclonal antibody, but this difference was not statistically significant. "But again, this agent has been shown to be safe in this patient population."

"Vedolizumab is one of the safest biologics that we have in the clinic … Findings from this study reinforce the safety profile of vedolizumab" despite the potential concerns regarding gastroenterological infection with the agent.

Dr. Dalal reported having no relevant conflicts of interest. Dr. Colombel has consulted for Takeda, which markets Entyvio for UC. Dr. Khanna has research grants from Rebiotix, as well as consulting fees from Shire Plc, Premier, Facile Therapeutics, and ProbioTech. ■

AGA Resource

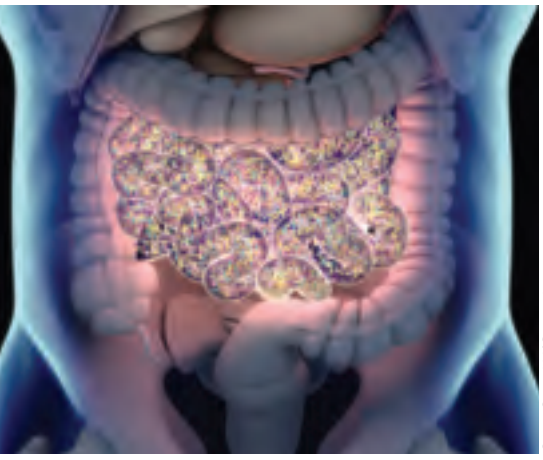
Help your patients understand their *C. difficile* diagnosis by sharing patient education from the AGA GI Patient Center: www.gastro.org/Cdiff.

Microbiota may predict success on low-FODMAP diet

BY HEIDI SPLETE
MDedge News

Two distinct gut microbiota subtypes showed an enhanced clinical response to a low-FODMAP diet in an analysis of 41 adults with irritable bowel syndrome (IBS) and household controls.

Irritable bowel syndrome has a significant impact on quality of life, and some patients find relief on a low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet, wrote Kevin Vervier, PhD, of Wellcome Sanger Institute, Hinxton, England, and colleagues. However, the mechanism of action for the success of low-FODMAP diets remains unclear, the diet is hard for many patients to follow, and the long-term impact on health is unknown. Therefore, research is needed to identify patients who would derive the most benefit, they wrote.



ChrisChrisW/Getty Images

In a study published in Gut (2021 Nov 22. doi: 10.1136/gutjnl-2021-325177), the researchers analyzed stool samples from 41 pairs of IBS patients and household contacts for response to a low-FODMAP diet. Stool samples were collected at baseline while on usual diets, and again after 4 weeks and 12 weeks on a low-FODMAP diet. The patients were divided into two groups based on microbiota clusters; baseline demographics and clinical characteristics were similar between the clusters. In addition, symptom severity was measured using the IBS Severity Scoring System (IBS-SSS).

Cluster 1 was referred to as IBS^P microbiome type because of its pathogenic properties, and cluster 2 as IBS^H microbiome type because of its resemblance to the microbiome of healthy household controls, the researchers wrote.

The IBS^P microbiomes were enriched in Firmicutes and in genes for amino acid and carbohydrate metabolism, at baseline, while the IBS^H microbiomes were similar to healthy controls.

After 4 weeks on the low-FODMAP diet, the IBS^P microbiomes normalized, with increased levels of Bacterioides and decreased levels of pathobionts (including *Clostridium difficile, Streptococcus parasanguinis, and Paeniclostridium sordellii*) to create a microbiome profile resembling the IBSH microbiomes and healthy controls. The taxonomic profile of microbiomes observed in IBS^H and healthy controls did not demonstrate a significant shift.

Although both microbiome groups showed improvement in IBS-SSS scores from baseline on the low-FODMAP diet, decreasing from a mean baseline score of 278 to a diet score of 128, the improvement was greater in the IBS^P group than the IBS^H group (delta, 194 vs. 114, respectively; $P = .02$), the researchers noted. "The shift in the IBS^P microbiota to a healthy profile appeared stable for at least 3 months and correlated with continuing symptomatic well-being," they wrote.

The distinct responses of the IBS^P and IBS^H microbiomes to the low-FODMAP diet suggest a potential mode of action, the researchers said in their discussion. Based on their findings, "it is possible that removal of the eliciting dietary component starves the pathobionts, leading to reduction in their growth and metabolism and a consequent decrease in symptoms, accompanied by an expansion of commensal or symbiotic species leading to a health-associated microbiome," but more research is needed to prove causality, they said.

The study findings were limited by several factors, including the relatively small sample size, strict inclusion criteria, restriction of medications, and need for participation by household controls, the researchers noted. Other limitations include the inability to control for other factors that could have impacted the gut microbiota, such as the placebo effect and psychological factors, they said.

However, the findings provide a foundation for more research and should be validated in other populations involving different geographical regions and dietary habits, they said. "The identification of a microbial signature 'biomarker' that correlates with improved response to a low-FODMAP diet may, if validated, allow better stratification and selection of patients likely to benefit from the diet," they concluded.

Setting the stage for focused studies

The low-FODMAP diet has demonstrated effectiveness for symptom relief in IBS, although potential risks include exacerbation of disordered eating, nutrition deficiencies, and disrupting gut microbiota, wrote Peter R. Gibson, MD, and Emma P. Halmos, MD, of Monash University and Alfred Health, Melbourne, in an accompanying editorial (Gut. 2021 Nov 22. doi: 10.1136/gutjnl-2021-326284). However, the current study takes a new step on the journey to identifying patients most likely to respond to a low-FODMAP diet, they said.

The editorialists noted three key takeaway points. First, the fecal microbiome may predict response to a low-FODMAP diet. Second, the correction of the microbiome through the low-FODMAP diet appeared to continue even after the diet was discontinued. "The other intriguing finding was that trehalose metabolic pathways were 'activated' in those with dysbiosis," suggesting that trehalose might be an unrecognized FODMAP, the researchers noted. Trehalose has not been well studied but has been associated with pathogenicity, they said.

Although the study may overemphasize the impact of the low-FODMAP diet given the relatively poor assessment of FODMAP intake, "the beauty of Vervier's work is not in its definitive nature but in that it enables the creation of feasible innovative hypotheses that can be examined by focused studies," they concluded.

The current study is important because IBS and related disorders of gut-brain interaction are common and greatly impact the quality of life of affected individuals, Jatin Roper, MD, of Duke University in Durham, N.C., said in an interview. Although the mechanisms for improvement are unknown, he said, "The low-FODMAP diet is widely used to treat IBS, based on the hypothesis that this diet modifies the gut microbiome in a beneficial way."

The study authors made two important discoveries, said Dr. Roper. "First, they found that they were able to distinguish IBS versus household controls based on their gut microbial signatures as well expression of key metabolic genes," he said. "Second, they identified a unique microbiota subtype that was associated with a significant clinical response to the low-FODMAP diet in IBS patients; IBS patients with a 'pathogenic' microbiome consisting of high Firmicutes and low Bacteroidetes responded to a greater degree to the low-FODMAP diet compared to IBS patients with a 'healthy' microbiome that was similar to controls," he explained. "Furthermore, after time on the low-FODMAP diet, the IBS patients with pathogenic microbiome signatures developed a microbiome with low Firmicutes and high Bacteroidetes, which is thought to be healthy," he added.

"These findings are exciting because they suggest that a patient's microbial signature might be used clinically to predict response to the low-FODMAP diet," said Dr. Roper. "The surprising aspect of these results is that the microbial signature alone was able to predict response to a low-FODMAP diet, despite the complex effects of the diet on host physiology and metabolism and the multifactorial etiology of IBS."

However, larger clinical studies are needed to confirm the study findings, Dr. Roper emphasized.

"This paper provides preliminary and provocative findings that suggest that gut microbiota metabolites may play a role in the pathogenesis of IBS," said Dr. Roper. "Future basic science and translational research is needed to study the mechanisms by which specific bacterial metabolites regulate intestinal function and disorders such as IBS," he said.

The study received no outside funding. Lead author Dr. Vervier had no financial conflicts to disclose. Dr. Gibson disclosed authoring two educational/recipe books on the low-FODMAP diet, and Monash University financially benefits from the sales of a digital application, booklets, and online courses on the low-FODMAP diet. Dr. Halmos had no financial conflicts to disclose. Dr. Roper had no financial conflicts to disclose. ■

AGA Resource

Through the AGA Center for Gut Microbiome Research and Education, AGA is committed to keeping you up-to-speed on the latest news, research and policy updates related to the gut microbiome: www.gastro.org/microbiome.

Margin marking before EMR cuts recurrence

BY MARCIA FRELLICK

Margin marking before endoscopic mucosal resection (EMR) of large colorectal polyps cut the risk of recurrence by 80% when compared with traditional EMR, new data suggest.

A team of researchers, led by Dennis Yang, MD, with the Center for Interventional Endoscopy at AdventHealth, Orlando, compared polyp recurrence after patients received EMR with margin marking versus recurrence after conventional EMR in a historical control group. They conclude that the simple margin-marking strategy may offer an alternative to margin ablation.

The findings of the study were published online Nov. 29 in Gastrointestinal Endoscopy (2021. doi: 10.1016/j.gie.2021.11.023).

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A single-center, historical control study

A total of 210 patients (average age, 66 years; 56.2% women) with 210 polyps (average size, 30 mm; interquartile range, 25-40 mm) had either EMR with margin marking (EMR-MM; n = 74) or conventional EMR (n = 136). The groups had similar patient and lesion characteristics.

For EMR-MM, cautery marks were drawn along the lateral margins of the polyp with the snare tip. EMR followed with resection of the healthy mucosa with the marks.

Physicians can confirm complete resection, including a healthy margin, when no cautery marks are visible after EMR, the authors wrote.

A follow-up colonoscopy was performed 3-6 months later, the results of which were compared against historical controls. After 6 months, EMR-MM led to a lower recurrence rate compared with the historical control group with traditional EMR (8% vs. 29%, respectively; $P < .001$).

"This strategy allowed a more reliable wide-field EMR, which may account for why our preliminary results demonstrated an 80% reduction in the likelihood of recurrence even after controlling for other factors, including polyp size and histopathology," the authors write.

Recurrence risk has been one of the main limitations of EMR compared with surgery, with rates from 10% to 35%, the authors note, though it has fewer adverse reactions and offers better quality of life than surgery.

Dr. Yang told this news organization that multiple studies have looked at possible factors for recurrence, which is thought to primarily occur at the lateral resection margins of the polyp.

"That's based on recent data that has shown that burning the resection margins after you actually take the lesion out reduces recurrence," he said. "What that indirectly implies is that whenever we resect something, we may think we've got the entire lesion at the lateral margins, but we don't."

As Dr. Yang described, it was this implication that led to the premise of the study.

Dr. Yang and colleagues also found that EMR-MM was not linked with an increase in adverse events. On multivariable analysis, EMR-MM was the main predictor of recurrence (odds ratio, 0.20; 95% confidence interval, 0.13-0.64; $P = .003$) aside from polyp size (OR, 2.81; 95% CI, 1.35-6.01; $P = .008$).

Expert: Standard of care likely still better

Gastroenterologist Douglas Rex, MD, Distinguished Professor Emeritus of Medicine at Indiana University School of Medicine, Indianapolis, who was not involved in the study, told this news organization that he is not convinced that it is necessary or wise to use the margin-marking technique described in the paper over the current standard of care.

Dr. Rex explained that currently, physicians inject large lesions submucosally with fluid colored for contrast to delineate the margin of the polyp. This raises the question: If you can see the lesion well with that method, do you need to place the marks before you start around the border on the normal mucosa, as they did for the margin-marking group in this study?

Dr. Rex also noted that the researchers' 29% control group recurrence rate is relatively high.

"Most of the evidence – if you look at the big meta-analyses – suggests that the recurrence rate with traditional methods is around 15%," he said.

He added that even the recurrence rate in the current study's active treatment arm is much higher than the 2%-5% rate seen in recent thermal ablation trials published in Gastroenterology by Klein and colleagues (2019 Feb;156[3]:604-13.e3) and Sidhu and colleagues(2021 Jul;161[1]:163-70.e3).

"What that indirectly implies is that whenever we resect something, we may think we've got the entire lesion at the lateral margins, but we don't."

"The methods described in those two papers should be considered the current standard of care," Dr. Rex said. "Neither one of those involves this [margin-marking] method."

Dr. Yang agrees that the those trials represent the standard of care but says it's important to note that the 2% recurrence may not represent the actual practice of endoscopists of all skill levels.

"These are highly controlled studies coming from very experienced endoscopists," he said.

"Our data are not trying to supplant what the high-quality studies on thermal ablation have shown. The point is to show that this is a concept that could potentially help," he said.

Dr. Rex said that a randomized control trial would clarify some points and be useful to compare margin marking directly with the current standard of care, "which is to remove the whole thing and then burn up the margin."

"Based on what we have seen so far, I would predict the current standard of care would have a very good chance of winning in terms of efficacy, because it's hard to get lower than 2% [recurrence]," he said. "And it might well win with regard to safety, because burning the margin is at least theoretically safer than what they're doing here."

Dr. Rex said margin marking may be beneficial with the form of EMR that does not involve submucosal injection: underwater EMR. In underwater EMR, there's no submucosal injection, and some people will mark the margin in those instances, he said.

"I do think it's reasonable to do margin marking for underwater EMR," Dr. Rex said.

Dr. Yang is a consultant for Boston Scientific, Olympus, Lumendi, and Steris. A coauthor is a consultant for Olympus, Boston Scientific, Cook Medical, Merit, Microtech, Steris, Lumendi, and Fujifilm. Another coauthor receives research grants from Steris and Cosmo/Aries Pharmaceuticals. Dr. Rex disclosed no relevant financial relationships. ■

Bulevirtide shows real-world efficacy versus HDV

BY JIM KLING
MDedge News

A real-world analysis of bulevirtide found a safety and efficacy profile similar to what was seen in earlier clinical trials in the treatment of hepatitis delta virus (HDV) infection.

HDV can infect only patients already carrying hepatitis B virus (HBV), but it causes the most severe form of viral hepatitis as it can progress to cirrhosis within 5 years and to hepatocellular carcinoma within 10 years.

Bulevirtide is a first-in-class medication that mimics the hepatitis B surface antigen, binding to its receptor on hepatocytes and preventing HDV viral particles from binding to it. The drug received conditional marketing approval by the European Medicines Agency in 2020 and has received a breakthrough therapy designation from the U.S. Food and Drug Administration.

The study was presented at the annual meeting of the American Association for the Study of Liver Diseases by Victor De Ledinghen, PhD, who is a professor of hepatology and head of the hepatology and liver transplantation unit at Bordeaux (France) University Hospital.

The early-access program launched after the French National Agency for Medicines and Health Products approved bulevirtide in 2019. It

Bulevirtide is a first-in-class medication that mimics the hepatitis B surface antigen, binding to its receptor on hepatocytes and preventing HDV viral particles from binding to it.

was made available to patients with compensated cirrhosis or severe liver fibrosis (F3) or patients with F2 fibrosis and alanine amino transferase levels more than twice the upper limit of normal for 6 months or more. Patients received bulevirtide alone (n = 77) or in combination with peg-interferon (n = 68), as determined by their physician.

The researchers defined virologic efficacy as HDV RNA levels being undetectable, or decreased by at least 2 $\log_{10}$ from baseline. They defined biochemical efficacy as ALT levels below 40 IU/L.

A per-protocol analysis included all patients in the bulevirtide group, but excluded 12 from the combination group who discontinued peg-interferon (n = 56). Nineteen patients in bulevirtide group had a treatment modification, and seven discontinued treatment. Five in the combination group had a treatment modification, and 14 stopped treatment. At 12 months, there was a greater decline in median $\log_{10}$ IU/mL in the combination group (–5.65 versus –3.64), though the study was not powered to compare the two. At 12 months, the combination group had 93.9% virologic efficacy, compared with 68.3% in the bulevirtide group.

The two groups had similar mean ALT levels at 12 months (48.91 and 48.03 IU/mL, respectively), with more patients in the bulevirtide group having normal ALT levels (<40 IU/L; 48.8% versus 36.4%). At 12 months, 39.0% of the bulevirtide group and 30.3% of the combination group had a combined response, defined as either undetectable HDV RNA or ≥2 $\log_{10}$ from baseline plus normal ALT levels.

Twenty-nine patients in the bulevirtide group had an adverse

"This [approval] was a very unusual step for the EMA to provide what is similar to emergency use approval while the phase 3 clinical trials are still ongoing."

event, compared with 43 in the combination group. The two groups were similar in the frequency of grade 3-4 adverse events (7 versus 6), discontinuation due to adverse events (2 versus 3), deaths (0 in both), injection-site reactions (2 in both), liver-related adverse events (4 versus 2), and elevated bile acid (76 versus 68).

During the Q&A period following the presentation, Dr. De Ledinghen was asked if he has a preferred regimen for HDV patients. "I think it depends on the tolerance of peg-interferon because of all the side effects with this drug. I think we need to have predictive factors of virological response with or without interferon. At this time, I don't have a preference, but I think at this time we need to work on predictive factors associated with virologic response," he said.

The EMA's conditional bulevirtide approval hinged on results from phase 2 clinical trials, while the phase 3 clinical studies are ongoing. "This was a very unusual step for the EMA to provide what is similar to emergency use approval while the phase 3 clinical trials are still ongoing," said Anna Lok, MD, who was asked to comment on the study. Dr. Lok is a professor of internal medicine, director of clinical hepatology, and assistant dean for clinical research at the University of Michigan, Ann Arbor.


Dr. Lok

She noted that the phase 2 studies indicated that the combination with peg-interferon seems to have an additive effect on HDV suppression, while monotherapy with bulevirtide has a greater effect on normalizing ALT levels. The real-world experience confirms these findings.

But the real-world data revealed some concerns. "What really worried me is the large number of patients who required dose modifications or discontinuations, and that seems to be the case in both treatment groups. They didn't really go into a lot of details [about] why patients needed treatment modifications, but one has to assume that this is due to side effects," said Dr. Lok.

She also noted that the per-protocol analysis, instead of an intention-to-treat analysis, is a weakness of the study. Additionally, over time, the number of patients analyzed decreased – as many as 40% of patients didn't have test results at month 12. "It makes you wonder what happened to those patients. Many probably didn't respond, in which case your overall response rate will be far lower," said Dr. Lok.

The study was funded by Gilead. Dr. De Ledinghen has financial relationships with Gilead, AbbVie, Echosens, Hologic, Intercept Pharma, Tillotts, Orphalan, Alfasigma, Bristol Myers Squibb, and Siemens Healthineers. Dr. Lok has no relevant financial disclosures. ■

Improving hepatic steatosis

RYGB *from page 1*

cardiovascular disease.

Moderate weight loss can clear liver fat and lead to histologic improvement of hepatic steatosis, and retrospective studies have suggested that RYGB may be more effective than SG and gastric banding in countering hepatic steatosis and steatohepatitis.

Dr. Hertel

At 1 year, both groups had similar percentage decreases in NAFLD liver fat score and NAFLD liver fat percentage.

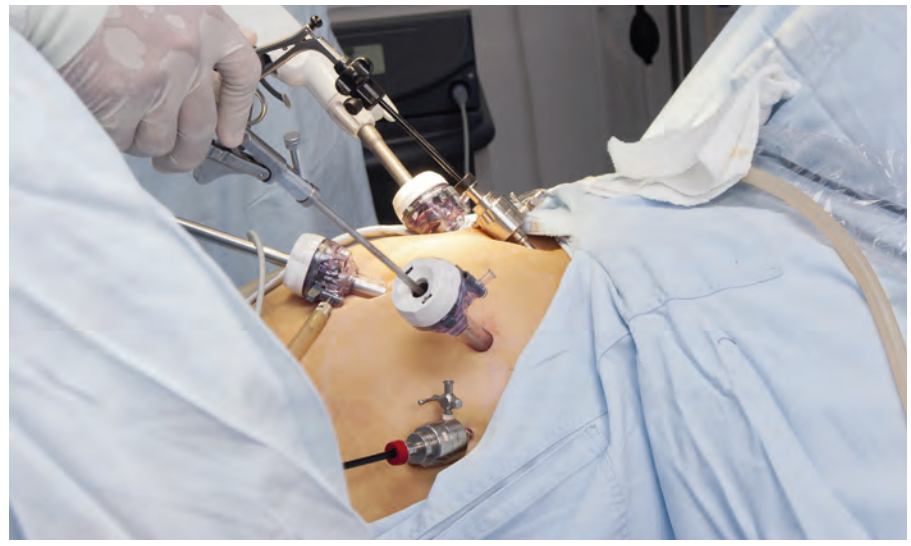
In fact, Dr. Aminian recently coauthored a paper (JAMA. 2021;326[20]:2031-42) describing results from the SPLENDOR study, which looked at 650 adults with obesity and nonalcoholic steatohepatitis (NASH) who underwent bariatric surgery at U.S. hospitals between 2004 and 2016, and compared liver biopsy outcomes to 508 patients who went through nonsurgical weight-loss protocols.

After a median follow-up of 7 years, 2.3% in the bariatric surgery group had major adverse liver outcomes, compared with 9.6% in the nonsurgical group (adjusted hazard ratio, 0.12; *P* = .01). The cumulative incidence of major adverse cardiovascular events (MACE) was 8.5% in the bariatric surgery group and 15.7% in the nonsurgery group (aHR, 0.30; *P* = .007). A total of 0.6% of the surgical group died within the first year after surgery from surgical complications.

Still, the question has not been tested in a randomized, controlled trial.

In the study published online in Annals of Internal Medicine (2021 Nov. doi: 10.7326/M21-1962), researchers led by Kathrine Aglen Seeberg, MD, and Jens Kristoffer Hertel, PhD, of Vestfold Hospital Trust, Tønsberg, Norway, conducted a prespecified secondary analysis of data from 100 patients (65% female, mean age, 47.5 years) with type 2 diabetes who had been randomized to undergo RYGB or SG between January 2013 and February 2018 at their center.

Prior to surgery, the mean liver fat fraction (LFF) was 19% (standard deviation, 12%). In the SG and RYGB groups, 24% and 26% of patients had no or low-grade steatosis (LFF ≤ 10%). LFF declined by 13% in both groups at 5 weeks, and by



HERJUA/THINKSTOCK

20% and 22% at 1 year, respectively, with no significant difference between the two groups.

At 1 year, 100% of the RYGB group had no or low-grade steatosis, as did 94% in the SG group (no significant difference). At 1 year, both groups had similar percentage decreases in the NAFLD liver fat score (between-group difference, –0.05) and NAFLD liver fat percentage (between-group difference, –0.3; no significant difference for either).

At baseline, 6% of the RYGB group and 8% of the SG group had severe fibrosis as measured by the enhanced liver fibrosis (ELF) test. At 1 year, the respective frequencies were 9% and 15%, which were not statistically significant changes.

There was much variation in ELF score changes between individuals, but 18% moved to a higher ELF category and only 5% improved to a lower ELF category at 1 year.

Limitations of the study include the fact that it was conducted at a single center and in a predominantly White population. The study also did not use liver biopsy, which is the standard for measuring fibrosis. Individuals with type 2 diabetes may have more severe NAFLD, which could limit the applicability to individuals without type 2 diabetes.

Together, the studies produce a clear clinical message, according to Dr. Aminian. "It provides compelling evidence for patients and medical providers that, if we can help patients lose weight, we can reverse fatty liver disease," he said.

The study was funded by the Southeastern Norway Regional Health Authority. Dr. Aminian has received research support from Medtronic. ■

DDSEP 9 Digestive Diseases Self-Education Program

Quick quiz answers

Questions on page 11.

Q1. Correct answer: E. Emergent angiography

Rationale

This patient presents with a massive lower GI hemorrhage. After a brisk upper GI bleed was ruled-out with esophagogastroduodenoscopy, the patient continued to hemorrhage and remained hemodynamically unstable. In the setting of a patient with ongoing massive lower GI bleeding who has been ruled out for an upper GI bleed (negative upper endoscopy) and who continues to have hemodynamic instability despite resuscitation, emergent angiography should be pursued in an effort localize and control bleeding.

Answer A is incorrect because an INR less than 2.5 does not require reversal prior to attempts at hemostasis. Answers B and C are incorrect because, given the patient's altered mental status and hemodynamic changes, she is unlikely to tolerate a bowel preparation and urgent colonoscopy. Also, there is no role for an unprepped colonoscopy in lower GI bleeding because of low yield and poor visualization. Answer D is incorrect because a nuclear-tagged red blood cell scan should be reserved for a patient who is hemodynamically stable.

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Q2. Correct answer: B. He should undergo surveillance colonoscopy now and annually thereafter.

Rationale

PSC diagnosis is the most consistent risk factor for colorectal cancer (CRC) in patients with inflammatory bowel disease. Other identified risk factors include endoscopic extent of the disease (pancolitis), duration of the disease (more than 8 years), age at diagnosis (young), presence of pseudopolyps, and family history of CRC. The current guidelines recommend first surveillance colonoscopy 8-10 years after the diagnosis of ulcerative colitis or Crohn's disease that involves more than one-third of the colon with subsequent surveillance intervals at 1-3 years. However, for patients with a concomitant diagnosis of PSC, the recommendation is to initiate surveillance as soon as the coexisting diagnosis is established, with annual surveillance colonoscopy thereafter.

High-dose UDCA (more than 28 mg/kg per day) is not recommended in patients with PSC because it was linked to adverse outcomes in this population including decompensated cirrhosis, death, and increased risk of colorectal neoplasia. On the other hand, low-dose UDCA may improve laboratory markers of cholestasis, but with no clear impact on survival or long-term outcomes, its role for chemoprophylaxis in colorectal cancer is still controversial. Yearly MRCP is recommended to screen for cholangiocarcinoma.

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THE TRUE IMPACT OF BOWEL URGENCY

UNDERSTANDING IT BEGINS WITH ASKING

SOME PATIENTS WITH ULCERATIVE COLITIS ARE TOO EMBARRASSED TO BRING UP BOWEL URGENCY.[1,2]* LIKE SARA, WHO CHANGED JOBS BECAUSE OF HER COMMUTE.[1,3,4†]

ASK ABOUT URGENCY AT EVERY VISIT

ONE SIMPLE QUESTION MAY MAKE A DIFFERENCE.[1,2]

ASKABOUTURGENCY.COM

*Studies were conducted in Japan (n=501) and Poland (n=71).

†The study was conducted in Ireland with 247 patients; Crohn's disease (n=162) and ulcerative colitis (n=85). Absenteeism from work/education due to illness/flare-up (n=139/240); withdrawal from work/education due to illness/flare-up (n=58/240).

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