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# GI&Hepatology News

January 2023

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University of Miami Miller School of Medicine Sylvester Comprehensive Cancer Center

Member SPOTLIGHT

Dr. Patricia Denise Jones is an associate professor and hepatologist at the University of Miami Health system.

## Miami hepatologist leverages Golden Rule to find balance

**BY JENNIFER LUBELL**

*MDedge News*

Hepatologist Patricia Denise Jones, MD, recollects the balancing act of going through medical training while caring for her four children.

"I had them at every stage: my first one as a medical student; twins when I was a resident, and my last one at the end of fellowship. It was challenging, trying to put their needs first while trying to be a great doctor, learning how to do research," said Dr. Jones, an associate professor at the University of Miami Health system.

She has no regrets. "I think I'm a better doctor and colleague because I have children. Showing my kids how important it is to help and serve others is one of the best legacies I can leave them."

If there's anything she'd like to fix, it's the health care delivery system for patients disproportionately affected by liver disease.

Dr. Jones was selected as 1 of 10 scholars in the

*See* **BALANCE** · *page 7*

## FDA OKs first fecal microbiota therapy for recurrent *C. diff*

*Approved for use after antibiotics*

**FROM STAFF REPORTS**

The Food and Drug Administration has approved the first fecal microbiota product to prevent recurrence of *Clostridioides difficile* infection (CDI) in people aged 18 years and older.

Rebyota (fecal microbiota, live-jslm), from Ferring Pharmaceuticals, is intended for use after an individual has completed antibiotic treatment for recurrent CDI. It is not indicated for the first occurrence of CDI.

"Recurrent CDI impacts an individual's quality of life and can also potentially be life-threatening," Peter Marks, MD, PhD, director, FDA Center for Biologics Evaluation and Research, said in a statement announcing approval.

As the first FDA-approved fecal microbiota product, this approval "represents an important milestone, as it provides an additional approved option to prevent recurrent CDI," Dr. Marks added.

A panel of FDA advisers recommended approval of Rebyota in September.

The application for Rebyota received priority review and had orphan drug and breakthrough therapy designation.

*See* **MICROBIOTA** · *page 7*

## Good news, bad news for GI in 2023

**FROM STAFF REPORTS**

Medicare expanded coverage of colorectal cancer (CRC) testing through the 2023 physician payment rule while also finalizing certain mandated budget cuts. AGA and its sister societies praised the federal plan to increase access to screening but are among the groups now calling on Congress to prevent pay decreases.

The 2023 Medicare Physician Fee Schedule (MPFS) lowers the minimum age for CRC screening to 45 from 50 years, in keeping with the recommendation from the U.S. Preventive Services Task Force. The physician payment rule, which was unveiled on Nov. 1, also ends the copay for colonoscopies that follow a positive stool-based

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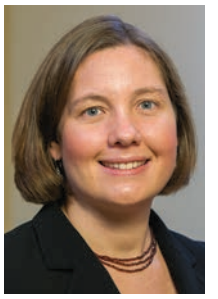
## LETTER FROM THE EDITOR

# *Building community: Introducing the new Member Spotlight column*

**BY MEGAN A. ADAMS, MD, JD, MSC**

Happy New Year, everyone! In early December, I attended the 2022 AGA Women's Leadership Collaboration Conference to discuss strategies to promote gender equity in our profession. It was an inspiring weekend and reminded me how many talented individuals we have in the field of gastroenterology, all with fascinating personal and professional stories and much to contribute. I think I speak for all attendees in saying that it was a privilege to have the opportunity to interact with this amazing group of women leaders, reflect on our shared experiences and visions for the future of GI, and expand our networks.

This month we are excited to launch a new recurring feature in the newspaper and online – the Member Spotlight column. AGA has more than 16,000 members from varied backgrounds. Yet the reality is that each of our individual networks is much smaller, and we would all benefit from learning more about one other and building a greater sense of community. To that end, starting with this issue, we will feature a different AGA member each month in our Member Spotlight column. The goal of this new feature is to recognize AGA members' accomplishments across all career stages and practice settings, to highlight the diversity of our membership, and to help AGA members feel more connected by learning more about each other. Our inaugural Member Spotlight column highlights Patricia Denise Jones, MD, associate professor at the University of Miami and an accomplished hepatologist. We thank Dr. Jones for sharing her story with us.



Dr. Adams

This will be a recurring monthly feature, so please consider nominating your colleagues (including trainees, practicing GIs in academics and community practice, those with nontraditional careers or unique pursuits outside of medicine, and others) to be featured in future Member Spotlight columns! It's a great way for the nominee's accomplishments to be recognized and to build a sense of community among the broader AGA membership. To submit a nomination, please send the nominee's name, email, and a brief description of why you are nominating them to: GINews@gastro.org. We look forward to reviewing your submissions and hope you will use these Member Spotlights as an opportunity to strike up a conversation with someone new and expand your networks. ∎

**"Please consider nominating your colleagues (including trainees, practicing GIs in academics and community practice, those with nontraditional careers or unique pursuits outside of medicine, and others) to be featured in future Member Spotlight columns!"**

*Megan A. Adams, MD, JD, MSc*
*Editor in Chief*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# Making a difference

**BALANCE** *from page 1*

inaugural cohort of the National Institutes of Health–funded program Fostering Opportunities Resulting in Workforce and Research Diversity (FORWARD) where she participated in a 2-year program of leadership development, mentorship, and research skills development.

In an interview, Dr. Jones discussed her life's work to address and research disparities in liver disease and cancer – and the motto that gets her through every day.

**"It's always rewarding to help someone make a connection that they couldn't make on their own... . Knowing that you're helping someone to live a healthier life is deeply gratifying."**

**Q:** Describe your current practice. What gives you the most joy in your day-to-day practice?
**Dr. Jones:** Being able to make a difference in the lives of patients. A lot of the patients that I take care of have difficulty navigating the health system. That's the population I feel most inclined to serve. It's always rewarding to help someone make a connection that they couldn't make on their own or help them understand something that wasn't clear. Knowing that you're helping someone to live a healthier life is deeply gratifying.

**Q:** Tell me about your patient population.
**Dr. Jones:** My focus is patients with liver cancer, hepatocellular carcinoma specifically, and cirrhosis patients. They tend to be sick relative to most Americans. I also take care of people who have other forms of liver disease like fatty liver and viral hepatitis. I live in Miami, so most of the patients that I take care of are going to be Hispanic. A good percentage are immigrants with limited health literacy.

**Q:** What is your biggest practice-related challenge? What are you doing to address it?
**Dr. Jones:** Lack of insurance and underinsurance. One patient of mine with Medicare and Humana has a carve out: She can see me and some of my colleagues but not the oncologist or a radiation oncologist. For her to be seen in our center, she would have to get a referral from a doctor in a different county. This makes no sense. It's a hard problem to solve. To me, that's the most challenging thing – not being able to help when something is beyond my control, beyond what I understand, and translating it into action.

**Q:** What general principles guide you in your professional and personal life?
**Dr. Jones:** I try to think of the Golden Rule in every encounter with a person, either in clinic or in real life, as if they were my mother or sister. If I'm frustrated or having a bad day, what would I want that person's experience to be with their doctor? I also try to assume the best possible intent with people.

**Q:** What teacher, mentor, or other influences had the greatest impact on you?

Courtesy Dr. Latosha Y. Flowers

Tanzania is Dr. Patricia Denise Jones's favorite travel destination.

**Dr. Jones:** My father. He started out as a salesman, worked in legislation, and then retired early to focus on and build up our community, making sure that we were better off than we were before. In terms of my professional life, Robert Sandler, MD, is one of my greatest mentors. He is at the University of North Carolina and was the division chief of gastroenterology. He saw potential in me and supports me to this day. If you need something, he's there. If you need him to comment on your draft, he's very reliable and gives you great, critical feedback.

**Q:** In 10 years, what do you hope you are doing or what do you hope you have accomplished?
**Dr. Jones:** In 10 years, I hope that my efforts will have revolutionized our approach to delivering care to vulnerable populations. Much of the work that has been done thus far in the field of disparities and liver disease has focused on describing the inequities. However, I have just started working in health equity. This will require partnering with patients and caregivers to get a better understanding of their needs and collaborating with legislators to increase funding directed towards building the infrastructure necessary to deliver health care to those who have been forgotten. ■

*Dr. Jones is on Twitter @DrLiverPatty.*

## Lightning round questions

**Favorite movie, show, or book**
*Forrest Gump, Blackish, anything by Toni Morrison*

**Favorite music genre**
*Hip Hop*

**Favorite food**
*Seafood*

**Favorite travel destination**
*Tanzania*

**Your ideal type of pet**
*Dog*

**Optimist or pessimist?**
*Optimist!*

# FDA approval

**MICROBIOTA** *from page 1*

### A vicious cycle

Treatment options for recurrent CDI are limited. It's been estimated that up to one-third of CDI cases recur, and people who suffer a recurrent bout of CDI are at a significantly higher risk for further infections.

Following the first recurrence, up to two-thirds of patients may experience a subsequent recurrence. Antibiotics used to treat CDI may contribute to a cycle of recurrence by altering the gut flora. The administration of fecal microbiota helps restore the gut flora to prevent further episodes of CDI.

"This is a major milestone in the translation of gut microbiome science to clinical solutions for patients," Phillip I. Tarr, MD, chair of the American Gastroenterological Association's Center for Gut Microbiome Research and Education Scientific Advisory Board, said in a written statement issued by the AGA. "This accomplishment is based on decades of work on the gut microbiome by gastroenterologists and collaborators. AGA applauds FDA for recognizing the demonstrated and conceptual merit of microbiota-based therapies."

Rebyota is a microbiota-based live biotherapeutic prepared from human stool collected from prescreened, qualified donors. It comes prepackaged in a single dose that is administered rectally.

The safety and efficacy of Rebyota were assessed in five clinical trials with more than 1,000 participants, the company notes in a press release.

In one trial, following a standard course of antibiotics, a one-time treatment with Rebyota was successful for three-quarters of participants at 8 weeks.

The treatment also prevented additional bouts; 84% of these initial responders remaining free of CDI at 6 months.

Two-thirds of participants reported treatment-emergent adverse events. Most events were mild to moderate in severity. Diarrhea and abdominal pain were the most common.

The data, from the ongoing PUNCH CD3-OLS study, were presented in October at the annual meeting of the American

*Continued on following page*

# CMS changes in 2023

**NEWS** *from page 1*

colon cancer test. However, it is important to note that colonoscopies that involve polyp removal are still subject to Medicare coinsurance requirements, although the financial responsibility eventually diminishes to zero by 2030: From 2023 to 2026, patient responsibility is 15% of the cost; from 2027 to 2029, it falls to 10%; and by 2030, it will be covered 100% by Medicare.

These changes come after a year of intense advocacy led by AGA, including multiple meetings with senior officials at the Centers for Medicare and Medicaid Services (CMS) and legislative pressure by members across the country. In the 2023 MPFS proposed rule, CMS attributed its decision to expand Medicare benefits to colonoscopy following a positive stool test to involvement from AGA, saying, "We consulted with and reviewed recommendations from a number of professional societies in developing this proposal, including supportive letters and communications with representatives from American Gastroenterological Association, American Cancer Society, and Fight Colorectal Cancer."

**These changes come after a year of intense advocacy led by AGA meeting with senior officials at CMS and legislative pressure by members across the country.**

"This is a win for all patients and should elevate our nation's screening rates while lowering the overall cancer burden, saving lives. Importantly, the changes will lessen colorectal cancer disparities, eliminating a financial burden for many patients," says AGA President John M. Carethers, MD, AGAF, who met with CMS earlier this year to advocate for the coverage of colonoscopy following a positive noninvasive colorectal cancer screening test.

David Lieberman, MD, AGAF, who met with CMS officials multiple times, offered, "Cost-sharing is a well-recognized barrier to screening and has resulted in disparities. Patients can now engage in a CRC screening program and be confident that they will not face unexpected cost-sharing for colonoscopy after a positive noninvasive screening test."

### 'Déjà vu all over again'

CMS uses its annual updates of the Physician Fee Schedule to make myriad policy decisions, with the 2023 version of the rule running close to 3,000 pages. AGA's summary of the 2023 MPFS final rule highlights changes that impact gastroenterologists.

But the most controversial provisions in the rule involve federal mandates meant to control spending that CMS has no control over. These include a reduction in one of the variables used in determining payment, known as the conversion factor. This will fall by $1.55 from the current level of $34.61 to $33.06 in 2023.

There's widespread agreement that Congress needs to reconsider its approach to setting Medicare payment for clinicians.

Between 2003 and April 2014, Congress passed 17 laws overriding the cuts to physician pay that were required under the old sustainable growth rate (SGR) formula.

The Medicare Access and CHIP Reauthorization Act of 2015 was supposed to end the annual battles over reimbursement cuts resulting from the SGR formula by changing the way physician payment is updated each year.

However, physicians face a 4.42% Medicare payment cut under the new payment system, as reflected in 2023 payment rule.

Two physicians serving in Congress, Rep. Ami Bera, MD (D-Calif.), and Rep. Larry Bucshon, MD (R-Ind.), have introduced legislation that would block next year's cuts.

The current fight to stave off 2023 cuts seems like "déjà vu all over again," said Kathleen Teixeira, AGA's vice president of government affairs, in an interview with this news organization. Congress needs to shift away from the "Band-Aid approach" and concentrate on longer-term issues with physician payment, she said.

Rep. Bera and Rep. Buchson in September 2022 issued a letter seeking feedback on ways to "stabilize the Medicare payment system" without dramatically increasing the cost to taxpayers.

Louis Wilson, MD, chair of the American College of Gastroenterology's legislative and public policy council, told this news organization that Congress needs to revisit Medicare's physician payment system, especially in terms of addressing inflation.

Lawmakers' attempts to restrain growth in Medicare physician payments have had the unintended consequence of fueling the acquisition of practices by hospitals, said Dr. Wilson, the managing partner of a physician-owned single-specialty private practice in Wichita Falls, Tex. Once doctors are employed by hospitals, Medicare often pays higher rates for their services than it would pay to physicians for providing the same care in a private practice.

**The FTC has said the U.S. physician workplace is "undergoing a dramatic restructuring," with traditional solo practices rapidly being replaced.**

Indeed, the Federal Trade Commission has said the U.S. physician workplace is "undergoing a dramatic restructuring," with traditional solo practices and small single-specialty group practices rapidly being replaced by large multispecialty physician group practices, or practices that are owned or employed by hospital systems. The FTC is in the midst of a major series of studies on the effects of this consolidation.

"There's been so much market distortion, so much limitation in innovation by failing to adequately pay in the Physician Fee Schedule, that the consequence is the widespread consolidation," said Dr. Wilson. "That's recognized on both sides of the aisle as being essentially expensive and inefficient and not in patients' best interest." ■

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*Continued from previous page*

College of Gastroenterology and were published simultaneously in the journal Drugs (2022 Oct 26. doi: 10.1007/s40265-022-01797-x).

"This is a positive adjunct to our current therapies for *C. difficile* in terms of trying to knock it out once a standard course of antibiotics has been administered," Lisa Malter, MD, AGAF, a gastroenterologist and professor of medicine at New York University Langone Health, said in an interview.

Dr. Malter acknowledged that, because it's delivered rectally, there could be "some hesitation" on the patient's part to undergo the therapy.

However, *C. difficile* can be "excruciating" for patients, and they "may be more than willing to take [this agent] because it gets them feeling better," said Dr. Malter said, who reported no relevant financial relationships.

The AGA will continue to follow the long-term effectiveness and safety of patients receiving Rebyota, fecal microbiota transplant, and other microbiota-based therapies through its FMT National Registry, according to the AGA statement.

Full prescribing information for Rebyota is available online. ■

*For more information about CDI and FMT, visit patient.gastro.org.*

DDSEP10
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## Quick quiz

**Q1. Which proton pump inhibitor has the highest potency?**
A. Lansoprazole
B. Omeprazole
C. Pantoprazole
D. Rabeprazole

**Q2. The risk most likely to be attributed to proton pump inhibitor use is:**
A. Enteric infection
B. Dementia
C. Diabetes
D. Gastric cancer
E. Renal insufficiency

*The answers are on page 20.*

# NAFLD plus T2D: More disease burden, progression

**BY CAROLYN CRIST**
*MDedge News*

Among people with nonalcoholic fatty liver disease (NAFLD), the fibrosis progression rate was higher among those who also had diabetes, according to new findings presented at the annual meeting of the American Association for the Study of Liver Diseases.

NAFLD patients with type 2 diabetes progressed by one stage about every 6 years, compared with one stage about every 8 years among patients without diabetes, said Daniel Huang, MBBS, a visiting scholar at the University of California San Diego NAFLD Research Center and a transplant hepatologist at National University Hospital in Singapore.


Dr. Huang

"We now know that fibrosis stage is a major determinant of liver-related outcomes in NAFLD, as well as overall mortality," he said. "Liver fibrosis progresses by approximately one stage every 7 years for individuals with NASH [nonalcoholic steatohepatitis]."

Recent UCSD data have indicated that about 14% of patients over age 50 with type 2 diabetes have NAFLD with advanced fibrosis, he noted. Previous studies have shown that diabetes is associated with higher rates of advanced fibrosis, cirrhosis, and hepatocellular carcinoma, but limited data exist around whether the fibrosis progression rate is higher in diabetics.

### National study cohort

Dr. Huang and colleagues conducted a multicenter, multiethnic prospective cohort study within the NASH Clinical Research Network consortium to examine the fibrosis progression rate and the fibrosis regression rate among patients with or without diabetes. The study included adult participants at eight sites across the United States who had biopsy-confirmed NAFLD and available paired liver biopsies that were at least 1 year apart.

Clinical and laboratory data were obtained at enrollment and prospectively at 48-week intervals and recorded at the time of any liver biopsies. A central pathology committee conducted the liver histology assessment, and the entire pathology committee was blinded to clinical data and the sequence of liver biopsy. The fibrosis progression and regression rates were defined as the change in fibrosis stage over time between biopsies, measured in years.

**"We now know that fibrosis stage is a major determinant of liver-related outcomes in NAFLD, as well as overall mortality. Liver fibrosis progresses by approximately one stage every 7 years for individuals with NASH."**

The study comprised 447 adult participants with NAFLD: 208 patients with type 2 diabetes and 239 patients without diabetes, Dr. Huang said. The mean age was 51, and the mean body mass index was 34.7. The patients with diabetes were more likely to be older, to be women, and to have metabolic syndrome, NASH, and a higher fibrosis stage.

Notably, the median hemoglobin A1c among patients with diabetes was 6.8%, indicating a cohort with fairly well-controlled blood sugar. The median time between biopsies was 3.3 years.

### Difference in progression, not regression

Overall, 151 participants (34%) experienced fibrosis progression, the primary study outcome. In a secondary outcome, 102 participants (23%) had fibrosis regression. The remaining 194 participants (43%) had no change in fibrosis stage. About 26% of patients with types 2 diabetes progressed to advanced fibrosis, as compared with 14.1% of patients without diabetes.

Among all those with fibrosis progression, the rate was 0.15 stages per year, with an average progression rate of one stage over 6.7 years. For patients with diabetes, the progression rate was significantly higher at 0.17 stages per year, compared with 0.13 stages per year among patients without diabetes, Dr. Huang said. That translated to an average progression of one stage over 5.9 years for patients with diabetes and 7.7 years for patients without diabetes.

In contrast, the regression rate was similar between those with or without diabetes at baseline, at –0.13 stages per year for those with diabetes versus –0.14 stages per year for those without diabetes. The similar outcome translated to an average regression of one stage over 7.7 years among those with diabetes and 7.1 years among those without diabetes.

Type 2 diabetes was an independent predictor of fibrosis progression in NAFLD, in both unadjusted and multivariable adjusted models, including baseline fibrosis stage, Dr. Huang said. In addition, patients with diabetes had a significantly higher cumulative incidence of fibrosis progression at 4 years (23% versus 19%), 8 years (59% versus 49%), and 12 years (93% versus 76%).

The research team didn't find a significant difference in HbA1c as a predictor of fibrosis progression when using a cutoff of 7%.

"It is possible that poor glycemic control may accelerate fibrosis further, but we need studies to validate this," Dr. Huang said. "These data have important implications for clinical practice and clinical trial design. Patients with NAFLD and diabetes may require more frequent monitoring for disease progression."

The NASH Clinical Research Network consortium is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Huang has served on an advisory board for Eisai. The other authors declared various research support and advisory roles with numerous pharmaceutical companies. ■



# Vonoprazan promising for erosive esophagitis

**BY MEGAN BROOKS**
*MDedge News*

The oral potassium-competitive acid blocker (PCAB) vonoprazan was noninferior and superior to the proton-pump inhibitor (PPI) lansoprazole for erosive esophagitis, according to results of the phase 3 PHALCON-EE trial.

Vonoprazan achieved higher rates of healing and maintenance of healing than lansoprazole, with the benefit seen primarily in patients with more severe esophagitis.

The differences in healing rates were evident after 2 weeks of therapy and were maintained throughout the 24-week study, report Loren Laine, MD, AGAF, Yale University, New Haven, Conn., and colleagues.

The study was published online in Gastroenterology (2022 Oct 10. doi: 10.1053/j.gastro.2022.09.041).

### More potent acid suppression

Gastroesophageal reflux disease is one of the most common disorders of the gastrointestinal tract, and erosive esophagitis is its most common complication.

Although standard PPI therapy is effective for healing erosive esophagitis, some patients do not achieve success with this conventional treatment.

Studies suggest that lack of healing of erosive esophagitis with 8 weeks of PPI therapy can be expected in roughly 5%-20% of patients, with rates up to 30% reported in patients with more severe esophagitis.

The PCAB vonoprazan provides more potent inhibition of gastric acid than PPIs and is seen as a potential alternative. However, data on its efficacy for erosive esophagitis are limited, the authors note.

The PHALCON-EE trial enrolled 1,024 adults from the United States and Europe with erosive esophagitis without *Helicobacter pylori* infection or Barrett esophagus.

Participants were randomized to receive once-daily vonoprazan 20 mg or lansoprazole 30 mg for up to 8 weeks in the healing phase.

The 878 patients with healing

*Continued on following page*

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were then rerandomized to receive once-daily vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg for 24 weeks in the maintenance phase.

For healing by week 8, vonoprazan was noninferior to lansoprazole in the primary analysis and superior to lansoprazole in a predefined exploratory analysis (92.9% vs. 84.6%; $P < .0001$).

Secondary analyses showed that vonoprazan was noninferior to lansoprazole in mean 24-hour heartburn-free days and superior in healing at week 2 for grade C/D esophagitis (70.2% vs. 52.6%; $P = .0008$).

For maintenance of healing at week 24, vonoprazan was noninferior to lansoprazole in the primary analysis and superior on secondary analysis of healing (80.7% for vonoprazan 20 mg and 79.2% for vonoprazan 10 mg vs. 72.0% for lansoprazole; $P < .0001$ for both comparisons).

The most common adverse event reported in the healing phase was diarrhea and in the maintenance phase was COVID-19. Two deaths occurred, both from COVID-19, during the maintenance phase in the vonoprazan 20-mg group.

As expected, serum gastrin increased to a greater extent with vonoprazan than lansoprazole, with levels > 500 pg/mL in 16% of those taking 20 mg at the end of maintenance therapy, the authors report. After stopping vonoprazan, patients' gastrin levels dropped by roughly 60%-65% within 4 weeks.

## Promising new option

"PCABs are a promising new option," Avin Aggarwal, MD, who was not involved in the study, told this news organization.

They have a "more potent acid inhibitory effect" and have shown "superior healing of erosive esophagitis," said Dr. Aggarwal, a gastroenterologist and medical director of Banner Health's South Campus endoscopy services and clinical assistant professor at the University of Arizona in Tucson.

**The results of the PHALCON-EE trial "validate noninferiority of PCABs compared to standard PPI therapy in the Western population after being proven in multiple Asian studies."**

The results of the PHALCON-EE trial "validate noninferiority of PCABs compared to standard PPI therapy in the Western population after being proven in multiple Asian studies," he said.

Dr. Aggarwal noted that PCABs work the same way as PPIs, by blocking the proton pumps, but "the longer half-life of PCABs and action on both active and inactive proton channels result in greater acid inhibition."

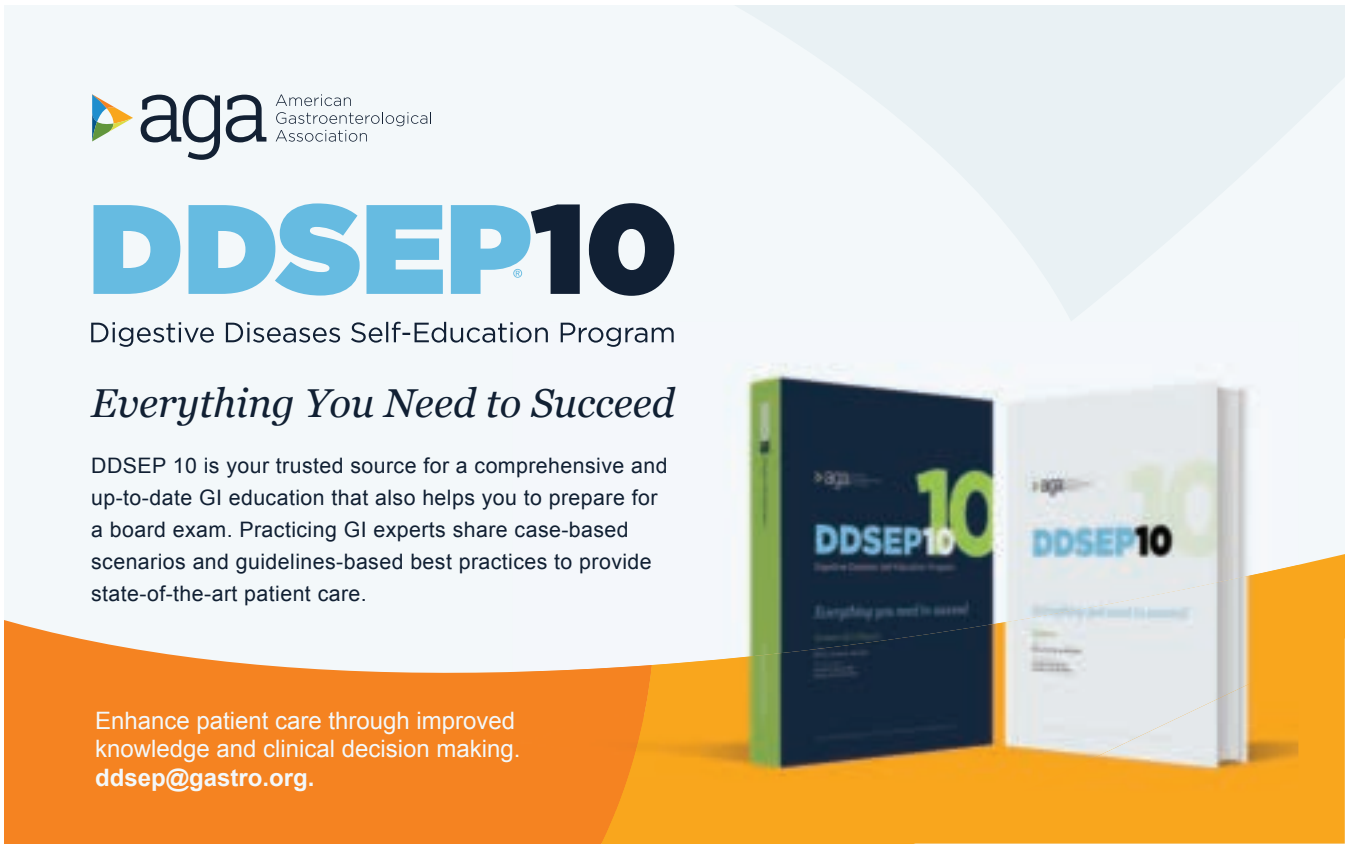
Long-term effects of PCAB therapy from stronger acid inhibition and resulting hypergastrinemia still remain to be determined, he said.

In March 2022, the U.S. Food and Drug Administration accepted Phathom Pharmaceuticals' new drug application for vonoprazan for the treatment of erosive esophagitis.

And in May, the FDA approved two vonoprazan-based therapies for the treatment of *H. pylori* infection.

The study was funded by Phathom Pharmaceuticals. Dr. Laine and several coauthors have disclosed financial relationships with the company. Dr. Aggarwal reports no relevant financial relationships. ■





# New algorithm for large nonpedunculated rectal polyps

**BY JIM KLING**
*MDedge News*

Large nonpedunculated rectal polyps (LNPRPs), defined as 20 mm or larger, are associated with a high risk of submucosal invasive cancer (SMIC). Although LNPRPs can be removed by distal colorectal surgery, this approach has an increased risk of morbidity, mortality, and permanent ostomy formation.

The first-line resection technique for LNPRPs is endoscopic mucosal resection (EMR); however, for larger lesions, piecemeal removal is required. When SMIC is revealed after piecemeal resection, surgery is generally recommended, since this is the only way to determine if R0 margins and curative oncologic resection have been achieved.

In such cases, an alternative is endoscopic submucosal dissection (ESD), but there is no current algorithm to choose between the two procedures based on lesion identity.

Optical methods can determine a lesion's pit and microvascular pattern in real time to determine if SMIC is present, but the performance is modest. Researchers sought to bolster optical detection by combining it with SMIC risk stratification to streamline the choice between EMR and ESD for LNPRPs.

In a study published online in Clinical Gastroenterology and Hepatology (2022 May 5. doi: 10.1016/j.cgh.2022.04.021), researchers led by Neal Shahidi, MD, of the division of gastroenterology, St. Paul's Hospital, Vancouver, described a selective resection algorithm (SRA) that could assist gastroenterologists in determining the best procedure to use when confronted with an LNPRP.

"Cost-effectiveness analyses have shown that an SRA using EMR and ESD is the optimal approach. However, a mechanism to facilitate modality selection has not been delineated. To our knowledge, this study is the first to show that a rectum-specific SRA, based on real-time optical evaluation and covert SMIC risk stratification, increases the frequency of curative oncologic resection and minimizes the risk of piecemeal resection of malignant LNPRPs. ... Piecemeal resection of endoscopically curable malignant LNPRPs negates the very benefit that they are intended to provide. To avoid malignant piecemeal resection, optical evaluation of the lesion's pit and microvascular surface pattern can be used to predict SMIC prior to resection technique selection," the authors wrote.

The researchers conducted a prospective observational study of 480 LNPRPs that were detected between July 2008 and April 2021. They compared the performance of the SRA to that of a universal EMR algorithm (UEA) for procedure determination. The SRA flagged LNPRPs with features consistent with SMIC (< 1,000 mm or Kudo pit pattern Vi) for endoscopic dissection. The latter included Paris 0-Is or 0-IIa+Is nongranular, or 0-IIa+Is granular with a dominant nodule 10 mm or larger. Other LNPRPs were designated to undergo EMR.

**There was no significant difference in recurrence at surveillance colonoscopy between SRA and UEA when undergoing margin thermal ablation.**

The median patient age was 67 years, and 54.2% were men; 90.1% of participants were ASA I-II; 290 LNPRPs were evaluated with the UEA and 190 with the SRA. The median lesion size was 40 mm. Overall, 11.7% of LPNRPs were identified as containing SMIC.

In the SRA, only 1.0% of LNPRPs removed by EMR contained SMIC, while the UEA identified cancer in 12.1%, a significant difference ($P$ = .001). The SRA led to 33.3% as curative oncologic resections, while the UEA achieved only 5.7% ($P$ = .010).

There were no significant differences in technical success or adverse events between the two algorithms.

Procedures determined by SRA took longer than those decided by UEA (median resection duration, 45 vs. 29 minutes; $P$ < .001). Among LNPRPs that were removed through EMR and margin thermal ablation, there was no significant difference in recurrence whether SRA or UEA was used to determine the procedure.

Compared with UEA, SRA was associated with higher rates of en bloc resection (90.5% vs. 11.4%; $P$ < .001), R0 resection (85.7% vs. 5.7%; $P$ < .001), and curative oncologic resection (33.3% vs. 5.7%; $P$ = .010).

"In this study, using analogous optical evaluation and covert SMIC risk stratification criteria, only one (1.0%) [of] malignant LNPRP underwent piecemeal resection within the SRA. This is a pivotal advance in the application of minimally invasive endoscopic resection techniques. It demonstrates an effective approach to optical evaluation; thereby, delineating which LNPRPs can be effectively, efficiently, and safely managed by EMR, compared with those which may derive benefit from ESD," the authors wrote.

The authors recommended ESD be used only for lesions with suspected superficial SMIC or when there is a heightened risk of SMIC.

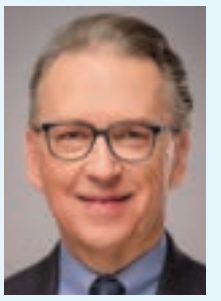
A key finding of the study is the frequency of curative resection following ESD. "At 33.3%, this represents a critical improvement in patient outcomes and the application of minimally invasive endoscopic resection techniques; especially when taking into consideration the potential negative ramifications of distal colorectal surgery and evidence showing that endoscopic resection does not impair subsequent surgical intervention," the authors wrote.

There was no significant difference in recurrence at surveillance colonoscopy between SRA and UEA when undergoing margin thermal ablation. The finding suggests that margin thermal ablation should be considered a vital component of EMR, according to the authors.

Dr. Shahidi received speaker honorarium from Boston Scientific and Pharmascience, and one coauthor received research support from Olympus, Cook Medical, and Boston Scientific. ■

In clinical practice there is widespread variation in the utilization of endoscopic submucosal dissection (ESD) versus endoscopic mucosal resection (EMR) for resection of large nonpedunculated rectal polyps (LNPRPs).

EMR is easier to learn and faster to perform than ESD and results in fewer perforations. EMR for LNPRPs is usually performed piecemeal, as opposed to ESD in which the goal is en bloc resection. When apparently successful piecemeal EMR is followed by cancer in the pathology report, surgical resection is frequently recommended. This is because assessment of residual cancer risk in the bowel wall or lymph nodes is often considered unachievable after piecemeal resection. Conversely, patients with superficial submucosal invasion after ESD may avoid surgical resection.


Dr. Rex

Much controversy surrounds which LNPRPs have a high enough risk of cancer, and/or the patient has a sufficiently high operative risk, so that the inefficiency and risk of ESD is justified to reduce surgeries that may follow piecemeal EMRs of malignant LNPRP. At one extreme of the opinion spectrum, all LNPRPs justify ESD.

This study describes a selective approach to colorectal ESD based on two factors. First, consider ESD primarily in the rectum where the morbidity of surgical resection is highest. Second, consider ESD for those rectal lesions where the cancer risk is highest, including lesions with surface pit and vascular patterns indicating high cancer risk and those with a sessile or nodular component. When this policy was used, only 1% of rectal EMRs were followed by a diagnosis of submucosally invasive cancer. This selective approach to colorectal ESD seems a reasonable combination of procedural efficiency and optimal patient outcomes.

*Douglas K. Rex, MD, MACP, MACG, MASGE, AGAF, is distinguished professor emeritus of medicine, Indiana University, Indianapolis. He serves as a consultant to Olympus, Boston Scientific, Aries Pharmaceutical, Braintree Laboratories, Lumendi, Norgine, Endokey, GI Supply, Medtronic, and Acacia Pharmaceuticals. He has received research support from EndoAid, Olympus, Medivators, Erbe USA, and Braintree Laboratories and is a shareholder in Satisfai Health.*

# Exosomes may drive HBV spread

**BY JIM KLING**
*MDedge News*

Hepatitis B virus, which can lead to acute and chronic hepatitis, infects more than 2 billion people worldwide, according to serological evidence. Although vaccines and treatments are available, there are approximately 1.5 million new HBV infections each year globally.

A new study has revealed a key step in the HBV life cycle: Researchers found that HBV virions can be released within exosomes, which are capable of infecting neighboring cells. The authors, led by Qingyan Wu of the department of virology, Paul-Ehrlich-Institut, Langen, Germany, suggest this strategy may help the virus escape immune surveillance and target a new hepatocyte.

**The researchers posit that LHBs could perform a similar function as classical hepatitis B surface antigens and filaments in foiling the immune response.**

The study was published online in Cellular and Molecular Gastroenterology and Hepatology (2022 Sep 30. doi: 10.1016/j.jcmgh.2022.09.012).

The researchers isolated exosomes from the supernatants of HBV-producing cells using exosomal and HBV markers. Electron microscopy using ultrathin sectioning along with immunogold labeling confirmed the presence of intact HBV virions in exosomes. The ultracentrifugation enabled the separation of the free virion fraction from the virions enclosed in exosomes. These findings fit in with previous discoveries of quasi-enveloped hepatitis A virus and hepatitis E virus.

The exosomes released free HBV virion and naked capsid after exposure to detergent. Cellular exposure to exosome morphogenesis inhibitors interfered with the release of exosome-packaged HBV. The researchers also observed large HBV surface antigens (LHB) on the external surface of the exosomes and found that the antigens allowed the exosome to infect susceptible cells through interaction with the sodium-taurocholate co-transporting polypeptide. LHB may also play an additional role in infectivity by countering the ability of antibodies to neutralize HBV.

However, the researchers also found that an LHB-specific neutralizing antibody inhibited infection of differentiated HepaRG cells with exosome-containing HBV. One explanation is that the antibody blocks the interaction between LHB and the target cell. Another is that the exosome disassembles near the target cell membrane and releases the virus, which is then blocked by the antibody since it can block entry of released virus.

To investigate the release pathway, the researchers used three different exosome-release inhibitors and found that all three interfered with HBV exosomal release. They also found that cells deficient in the exosome proteins Alix and syntenin did not release exosomal HBV.

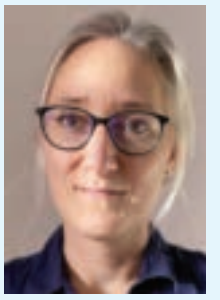
Alix appears to be involved in HBV exosomal release, as evidenced by the fact that release of exosomal HBV is boosted in Alix-deficient cells following rescue through overexpression of mCherry-Alix fusion construct. Overexpression of mCherry-Alix had no effect on release of free HBV virions.

The researchers also found evidence that two other exosomal proteins, CD63 and TSG101, play a role in incorporation of LHBs in the HBV envelope, as well as release of HBV through interactions with the protein alpha-taxilin. CD63 and TSG101 are also critical to the formation of exosomes, and the authors suggest further research into their functioning could be fruitful.

Whether exosome-released HBV results from crosstalk between the virus and host cells still needs to be determined. If host factors play a role in connecting HBV to exosomes, it will be interesting to work out which conditions trigger this process, as well as determine which events trigger the release of free virus through multivesicular bodies.

The researchers posit that LHBs could perform a similar function as classical hepatitis B surface antigens and filaments in foiling the immune response. Such a function would require that the virus escape from antibodies before opsonin proteins tag the antigens. It's also possible that LHBs enable infection of nonhepatic tissues, though this would likely be inefficient.

Viral cell entry and viral neutralization by antibodies are largely defined by the virion structure. Not surprisingly, viruses have evolved strategies to hijack cellular pathways for their morphogenesis to promote their dissemination and escape host immune responses. Hepatitis B viruses are released as infectious enveloped virions from infected cells through the multivesicular body pathway. Moreover, excess HBV envelope proteins are exported as noninfectious subviral particles that can act as decoys to trap neutralizing antibodies.


Dr. Zeisel

Using cell culture models, investigators from the Hildt lab show in this study that a minority of enveloped virions are released within exosomes, the biogenesis of which is closely linked to HBV morphogenesis. The authors report that exosome-associated HBV can infect HBV-susceptible hepatoma cells and thus contribute to viral dissemination. The molecular mechanisms underlying infection of target cells by exosome-associated HBV and virions are largely comparable.

There is no major alternative entry pathway for HBV transported by exosomes, thus they can be inhibited by antibodies directed against the large HBV surface antigen (LHB) and the entry inhibitor Myrcludex. In addition to its role in exosome-cell interaction, the LHB on the exosome surface represents a target for neutralizing antibodies and, by providing an alternative target for humoral responses, could contribute to the evasion of infectious virions. The relative contribution of exosomes to HBV dissemination vs. escape remains to be determined.

Studies using HBV derived from the blood of HBV-infected patients are required to assess the relevance of these processes in vivo and if/how these are affected by antiviral therapies.

*Mirjam B. Zeisel, PharmD, PhD, is with the Cancer Research Center of Lyon, Université de Lyon (France) and reports no conflicts of interest.*

Many other host proteins have been observed in exosomes released by HBV-infected hepatocytes, suggesting that host proteins may play other roles. A proteomics analysis found proteasome subunit proteins in HepAD38-derived exosomes. The authors suggest that those proteins may allow the exosomes to mediate transcellular immune regulation.

**Exosomes that carry HBV particles seem to have the potential to deliver HBV to nonpermissive cells with low efficiency. This suggests they could be an additional factor contributing to HBV spread.**

Subviral particles may enhance viral infection, and exosomes from HBV-positive cells may contribute, possibly through exosome surface LHBs, according to the authors. They found that an LHB-specific neutralizing antibody inhibited infection of differentiated HepaRG cells. One explanation is that the antibody blocks the interaction between LHB and the target cell. Another is that the exosome disassembles near the target cell membrane and releases the virus, which is then blocked by the antibody since it can block entry of released virus.

"This previously undiscovered strategy of sequestering HBV particles in exosomes could be a strategy to escape from the immune response and to target them, protected by the exosomal membrane, to the hepatocyte. Exosomes that carry HBV particles seem also to have the potential to deliver HBV to nonpermissive cells with low efficiency. This suggests that exosomes could be an additional factor that contributes to the spread of HBV," the authors wrote.

The authors had no financial conflicts. This research was funded by the LOEWE Center ACLF, DRUID, the Germany Research Foundation, and the China Scholarship Council. ■

*AGA Clinical Practice Update: Expert Review*

# Update focuses on acute kidney injury in cirrhosis

**BY LIAM DAVENPORT**
*MDedge News*

Acute kidney injury (AKI) in patients with cirrhosis is potentially preventable, and there are clear steps that can be taken to manage and reverse the condition, concludes a clinical practice update from the American Gastroenterological Association.

AKI occurs in 47% of patients hospitalized with complications of cirrhosis and in approximately 30% of outpatients with cirrhosis, resulting in a total cost in the United States of $4 billion, explained Patrick S. Kamath, MD, division of gastroenterology and hepatology, Mayo Medical School, Rochester, Minn., one of the authors of this update.

Moreover, Dr. Kamath told this news organization, among patients with cirrhosis and AKI, morbidity and mortality is sevenfold higher in comparison to those without cirrhosis, and repeated episodes of AKI increase the risk of progression to chronic kidney disease.

The authors conducted an expert review of the best available published evidence and gathered expert opinion. The update was published online in Clinical Gastroenterology and Hepatology (2022 Sep 6. doi: 10.1016/j.cgh.2022.08.033).

Along with some key takeaways (see box), the update also emphasizes the importance of an accurate diagnosis, inasmuch as not all cases of AKI are due to hepatorenal syndrome (HRS), for example. It goes on to advise that the specific type of AKI be identified through medical history and physical examination, as well as with blood biochemistry, urine microscopic examination, urine chemistry, selected urinary biomarkers, and renal ultrasound.

Additionally, it underscores the need to identify and treat infections and to closely monitor fluid status.

Nancy S. Reau, MD, AGAF, Rush Medical College, Chicago, who was not involved in the update, told this news organization that fluid status is important when giving albumin replacement therapy because of the increased risk for pulmonary edema.

She also highlighted that this update advises against transjugular intrahepatic portosystemic shunts (TIPSs) as a specific treatment for HRS-AKI, noting that, although the 2022 North American Practice-Based Recommendations for Transjugular Intrahepatic Portosystemic Shunts in Portal Hypertension do not advocate for TIPs for this indication, they also indicated that there was enough evidence to advise against it.

In other key best practice advice statements, the update advises clinicians to hold diuretics and nonselective beta-blockers and to discontinue nonsteroidal anti-inflammatory drugs.

Overall, Dr. Reau believes that the update is "timely, especially in light of the recent [U.S.] approval of terlipressin, which will change our treatment options." This update also supports the American Association for the Study of Liver Diseases 2021 Practice Guidance guidelines on HRS, she added.

Zobair Younossi, MD, MPH, of Virginia Commonwealth University, Inova Campus, Falls Church, who was not involved in writing the update, told this news organization that the update is important because of the huge increase in mortality among patients with cirrhosis and AKI.

Dr. Younossi said the update offers a very clearly stated algorithm for how to identify those patients whose condition is easily reversible with volume repletion, in comparison with those patients who require medical treatment or even liver transplantation.

"The key for clinicians is to make sure they understand, in the context of cirrhosis, some of the easy things that they can do to prevent AKI," he continued. He added that the use of NSAIDs in these patients is "going to be problematic."

Dr. Kamath reported having a relationship with Sequana Medical. Dr. Reau has relationships with Salix and Intercept. Dr. Younossi has disclosed no relevant financial relationships. ■

### Some key takeaways

Among its 14 best practice statements, the update describes three situations indicative of AKI:

- A serum creatinine increase of 0.3 mg/dL or more within 48 hours, or
- A serum creatinine increase of 50% or more from baseline, which is a stable serum creatinine in the past 3 months.
- Reduction in urine output of up to 0.5 mL/kg per hour for more than 6 hours.

➤ INTESTINAL DISORDERS

# Guselkumab and golimumab: Found better together for UC

**BY DAMIAN MCNAMARA**
*MDedge News*

CHARLOTTE, N.C. – Researchers compared the combination therapy of guselkumab and golimumab (both from Janssen) for 12 weeks, followed by guselkumab monotherapy up to week 38, versus either agent as monotherapy for the full 38 weeks in ulcerative colitis patients. The combination induction strategy "achieved higher rates of clinical remission, endoscopic improvement, composite endpoint of histologic remission, and endoscopic improvement," said Brian G. Feagan, MD, senior scientific director at the contract research organization Alimentiv and a gastroenterologist at Western University in London (Ont.).

The findings. presented at the annual meeting of the American College of Gastroenterology, are from a randomized, double-blind, study of 214 adults with moderately to severely active ulcerative colitis. Of the patients, 71 were randomly assigned to receive guselkumab, 200 mg intravenous at baseline and at weeks 4 and 8, plus 100 mg subcutaneous every 8 weeks. Another 72 patients received golimumab, 200 mg SC at baseline, and 100 mg SC at weeks 2, 6, and 10, and every 4 weeks thereafter. The combination group of 71 patients received guselkumab 200 mg IV and golimumab 200 mg SC at baseline, followed by golimumab 100 mg SC at weeks 2, 6, and 10, and guselkumab 200 mg IV at weeks 4 and 8. At week 12, this group switched to monotherapy with guselkumab, 100 mg SC every 8 weeks.


Dr. Feagan

The rate of clinical remission in the combination group was 44%. The rate was lower with guselkumab monotherapy at 31% and golimumab monotherapy at 22% at week 38. These percentages were based on a full Mayo score of 2 or less and no individual subscore greater than 1. At the same time, rates of clinical remission by modified Mayo score also favored the combination group at 48%, followed by 31% in the guselkumab group and 21% in the golimumab cohort.

Endoscopic improvement, endoscopic normalization, histologic remission, and composite histologic-endoscopic endpoints were also greater in the combination group than in the monotherapy groups. "Quite striking differences were maintained up to week 38," Dr. Feagan said. "This combination treatment warrants further investigation, and phase 3 trials are underway."

"The early study results, such as the VEGA study, appear promising for combination biologics with a good safety profile," Jean-Paul Achkar, MD, staff physician in the Center for Inflammatory Bowel Disease at Cleveland Clinic, said when asked to comment. "These data are particularly valuable as we have seemingly reached a therapeutic response ceiling for single-biologic therapy, and we need to determine the added benefit and safety profile of a combination of two biologics or the combination of a biologic and a small molecule," added Dr. Achkar, who served as the session comoderator.

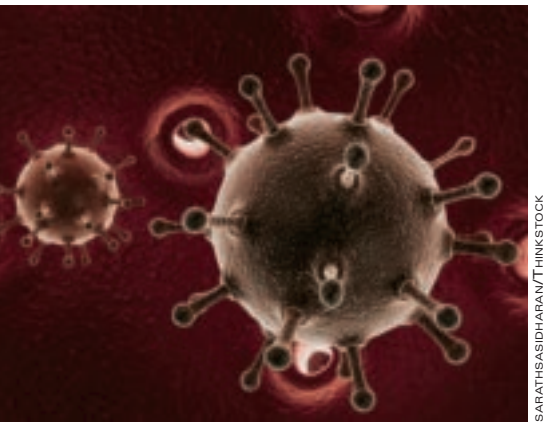
The study was funded by Janssen Research and Development. Dr. Feagan reports consultanting for Janssen. Dr. Achkar had no disclosures. ■

# Bepirovirsen: Is there a 'functional' cure for HBV on the horizon?

**BY MEGAN BROOKS**
*MDedge News*

Treatment with bepirovirsen led to sustained clearance of hepatitis B surface antigen (HBsAg) and hepatitis B virus DNA for 24 weeks after the end of treatment for adults with chronic HBV in the phase 2b B-Clear study.

The study results were presented at the annual meeting of the American Association for the Study of Liver Diseases and were simultaneously published in the New England Journal of Medicine (2022 Nov 8. doi: 10.1056/NEJMoa2210027).



SARATHSASIDHARAN/THINKSTOCK

Currently, nucleoside/nucleotide analogue (NA) therapy is the recommended first-line therapy for patients with chronic HBV because it can inhibit viral replication.

However, fewer than 5% of patients have HBsAg loss after 12 months of NA therapy, which underscores the need for therapies that can achieve a "functional" cure, largely defined as sustained, undetectable levels of HBV DNA and HBsAg in the blood, with or without generation of protective antibodies against HBsAg, the researchers noted.

Bepirovirsen is a potential first-in-class antisense oligonucleotide that targets all HBV messenger RNA and acts to decrease levels of viral proteins.

The phase 2b B-Clear study enrolled 457 patients with chronic HBV; 227 were receiving NA therapy, and 230 were not.

Participants were randomly assigned to receive weekly subcutaneous injections of bepirovirsen 300 mg for 24 weeks; bepirovirsen 300 mg for 12 weeks, then 150 mg for 12 weeks; bepirovirsen 300 mg for 12 weeks, then placebo for 12 weeks; or placebo for 12 weeks, then bepirovirsen 300 mg for 12 weeks (groups 1, 2, 3, and 4, respectively).

The composite primary outcome was HBsAg level below the limit of detection and HBV DNA level below the limit of quantification maintained for 24 weeks after the end of bepirovirsen treatment, without newly initiated antiviral medication.

Bepirovirsen 300 mg weekly for 24 weeks (group 1) led to HBsAg and HBV DNA loss in 9% of patients receiving NA therapy and 10% of patients not receiving NA treatment, which was sustained for 24 weeks after the last dose.

For groups 2, 3, and 4, HBsAg and HBV DNA loss occurred in 9%, 3%, and 0%, respectively, of patients receiving NA therapy and 6%, 1%, and 0%, respectively, of patients not receiving NA treatment.

Patients with low baseline HBsAg levels (< 1,000 IU/mL) responded best to treatment with bepirovirsen. Among patients who received bepirovirsen 300 mg weekly for 24 weeks, the primary outcome was achieved by 16% of patients taking NA therapy and by 25% of patients not taking NA therapy.

Although a "relatively low percentage" of patients overall achieved the primary outcome, the study "indicates the possibility of enhanced efficacy with the selection of patients according to baseline characteristics (low HBsAg level at baseline), with combination therapies, or both," the researchers wrote.

Adverse events with bepirovirsen included injection-site reactions, pyrexia, fatigue, and increased alanine aminotransferase levels. Increases in ALT levels, which were more common in those not receiving NA therapy than in those receiving NA therapy (41% vs. 17%), led to two serious adverse events.

On the basis of phase 2b data, GlaxoSmithKline (GSK) plans to advance bepirovirsen into phase 3 development, according to a news release.

Further pursuit of bepirovirsen therapy is "certainly warranted, with the use of a dose of 300 mg per week for at least 24 weeks; indeed, the duration of therapy might be dictated best by HBsAg levels at baseline," Jay H. Hoofnagle, MD, director of the liver disease research branch at the National Institute of Diabetes and Digestive and Kidney Diseases, wrote in an editorial in the New England Journal of Medicine (2022 Nov 8. doi: 10.1056/NEJMe2213449).

Several critical questions remain, including whether HBsAg negativity will persist beyond 24 weeks, wrote Dr. Hoofnagle, who was not involved in the study.

It's a question GSK is addressing in the B-Sure trial, which will follow participants for an additional 33 months, the study noted.

Other questions include when NA therapy can be safely stopped, what other factors predict response, and whether RNA therapy–induced loss of HBsAg materially improves long-term outcomes, Dr. Hoofnagle wrote.

"Bepirovirsen is just one RNA-based HBV therapy now being pursued. Several other antisense RNAs as well as the more malleable small interfering RNA molecules ('-sirans') are currently in early-phase clinical trials. A new era in the control of hepatitis B may be at hand with these most modern of therapies for this most ancient disease," Dr. Hoofnagle noted.

The B-Clear study was supported by GSK. Several authors have disclosed relationships with the company. A complete list of author disclosures is available with the original article. Dr. Hoofnagle has disclosed no relevant financial relationships. ■

# Living-donor liver transplants on rise in urgent cases

**BY CAROLYN CRIST**
*MDedge News*

Living-donor liver transplants (LDLT) for recipients with the most urgent need for a liver transplant in the next 3 months – a model for end-stage liver disease (MELD) score of 25 or higher – have become more frequent during the past decade, according to new findings presented at the annual meeting of the American Association for the Study of Liver Diseases.

Among LDLT recipients, researchers found comparable patient and graft survival at low and high MELD scores. But among those patients who had high MELD scores, the researchers found lower adjusted graft survival and a higher transplant rate among those with living donors, compared with the recipients of deceased-donor liver transplantation (DDLT).

**"Historically, in the United States especially, living-donor liver transplantation has been offered to patients with low or moderate MELD. The outcomes of LDLT at high MELD are currently unknown."**

The findings suggest certain advantages of LDLT over DDLT may be lost in the high-MELD setting in terms of graft survival, said Benjamin Rosenthal, MD, an internal medicine resident focused on transplant hepatology at the Hospital of the University of Pennsylvania, Philadelphia.

"Historically, in the United States especially, living-donor liver transplantation has been offered to patients with low or moderate MELD," according to Dr. Rosenthal. "The outcomes of LDLT at high MELD are currently unknown."

Previous data from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) found that LDLT offered a survival benefit versus remaining on the wait list, independent of MELD score, he said.

A recent study also has demonstrated a survival benefit across MELD scores of 11-26, but findings for MELD scores of 25 and higher have been mixed.

Dr. Rosenthal and colleagues conducted a retrospective cohort study of adult LDLT recipients from 2010 to 2021 using data from the Organ Procurement and Transplantation Network, the U.S. donation and transplantation system.

In baseline characteristics among LDLT transplant recipients, there weren't significant differences in age, sex, race, and ethnicity for MELD scores below 25 or at 25 and higher. There also weren't significant differences in donor age, relationship, use of nondirected grafts, or percentage of right- and left-lobe donors for LDLT recipients. However, recipients with high MELD scores had more nonalcoholic steatohepatitis (29.5% versus 24.6%) and alcohol-assisted cirrhosis (21.6% versus 14.3%).

### Outcome and MELD scores in LDLT and DDLT recipients

The research team evaluated graft survival among LDLT recipients by MELD below 25 and at 25 or higher. They also compared posttransplant patient and graft survival between LDLT and DDLT recipients with a MELD of 25 or higher. They excluded transplant candidates on the wait list for Status 1/1A, redo transplant, or multiorgan transplant.

Among the 3,590 patients who had LDLT between 2010 and 2021, 342 patients (9.5%) had a MELD of 25 or higher at transplant.

There was some progression during the waiting period, Dr. Rosenthal noted, with a median listing MELD score of 19 among those who had a MELD of 25 or higher at transplant and 21 among those who had a MELD of 30 or higher at transplant.

For LDLT recipients with MELD scores above or below 25, researchers found no significant differences in adjusted patient survival or adjusted graft survival.

Then the team compared outcomes of LDLT and DDLT in high-MELD recipients. Among the 67,279-patient DDLT comparator group, 27,552 patients (41%) had a MELD of 25 or higher at transplant.

In terms of LDLT versus DDLT, unadjusted and adjusted patient survival were no different for patients with MELD of 25 or higher. In addition, unadjusted graft survival was no different.

However, adjusted graft survival was worse for LDLT recipients with high MELD scores.

In addition, the retransplant rate was higher in LDLT recipients, at 5.7% versus 2.4%.

The reason why graft survival may be worse remains unclear, Dr. Rosenthal said. One hypothesis is that a low graft-to-recipient weight ratio in LDLT can cause small-for-size syndrome. However, these ratios were not available from OPTN. "Further studies should be done to see what the benefit is, with graft-to-recipient weight ratios included," he said. "The differences between DDLT and LDLT in this setting should be further explored as well."


Dr. Rosenthal

The research team also described temporal and transplant center trends for LDLT by MELD group. For temporal trends, they expanded the study period from 2002 to 2021. They found a marked U.S. increase in the percentage of LDLT with a MELD of 25 or higher, particularly in the last decade and especially in the last 5 years. But the percentage of LDLT with high MELD remains lower than 15%, even in recent years, Dr. Rosenthal noted.

**The percentage of LDLT with high MELD remains lower than 15%, even in recent years.**

Across transplant centers, there was a trend toward centers with increasing LDLT volume having a greater proportion of LDLT recipients with a MELD of 25 or higher. At the 19.6% of centers performing 10 or fewer LDLT during the study period, none of the LDLT recipients had a MELD of 25 or higher, Dr. Rosenthal said.

The authors didn't report a funding source. The authors declared no relevant disclosures. ■

# Multiple options available for treating obesity

*Dear colleagues,*

Treating obesity easily falls under our purview as gastroenterologists. But like the mouse who would bell the cat, our direct involvement has been limited. However, over the past decade, advances in endobariatrics and medical management have given us many options. But how do we choose from this growing armamentarium of minimally invasive procedures and weight-loss medicines? What combination is best? And what about the standard "diet and exercise"?

In this issue of Perspectives, Carolyn Newberry, MD, director of GI nutrition at Innovative Center for Health and Nutrition in Gastroenterology, Weill Cornell Medicine, New York, will emphasize the benefits of medical and lifestyle management.

Pichamol Jirapinyo, MD, MPH, ABOM, director of bariatric endoscopy fellowship at Brigham and Women's Hospital/Harvard Medical School, Boston, responds with robust data for endoscopic therapies.

We hope that their expert perspectives will help guide you in your own approach to obesity management – certainly no one size fits all. I welcome your thoughts on this growing field in gastroenterology – share with us on Twitter @AGA_GIHN.


Dr. Ketwaroo

*Gyanprakash A. Ketwaroo, MD, MSc, is chief of endoscopy at West Haven (Conn.) VA Medical Center. He is an associate editor for GI & Hepatology News.*

## Exciting time for endoscopic bariatric and metabolic therapies

**BY PICHAMOL JIRAPINYO, MD, MPH, ABOM**

2022 was an exciting year for our field of endoscopic bariatric and metabolic therapy (EBMT). Currently, at our institution, we offer four primary EBMTs for patients who are seeking endoscopic weight loss therapy and have not yet undergone prior bariatric surgery. These include the Orbera intragastric balloon (IGB Apollo Endosurgery), (endoscopic sleeve gastroplasty; Apollo Endosurgery), primary obesity surgery endoluminal (POSE; USGI Medical, San Clemente, Calif.), and a gastric plication procedure using Endomina (Endo Tools Therapeutics, Gosselies, Belgium). While the former two have Food and Drug Administration approval, the latter two devices have FDA clearance for tissue approximation. The indication for primary EBMTs includes having a body mass index of at least 30 kg/m$^2$.


Dr. Jirapinyo

During the initial consultation, I always discuss pros and cons of all treatment modalities for obesity with the patients, ranging from lifestyle modification to antiobesity medications (AOMs), EBMTs, and bariatric surgeries. While the data on antiobesity medications are promising, especially with the most recent FDA-approved semaglutide (Wegovy: Novo Nordisk, Bagsvaerd, Denmark) yielding 14.9% total weight loss at 1 year, in reality, the starting doses of this medication have been out of stock for over a year. Other AOMs, on the other hand, are associated with 6%-8% TWL and are frequently associated with intolerance due to side effects. In comparison, meta-analyses demonstrate that an IGB is associated with 11.3% TWL and ESG with 16.5% TWL at 1 year.

*Dr. Jirapinyo is the director of bariatric endoscopy fellowship at Brigham and Women's Hospital/Harvard Medical School, Boston. She is board certified in internal medicine, gastroenterology, and obesity medicine and completed her bariatric endoscopy and advanced endoscopy fellowships at Brigham and Women's Hospital. She serves as a consultant for Apollo Endosurgery, Spatz Medical, and ERBE, and she receives research support from USGI Medical, GI Dynamics, and Fractyl.*

## A new frontier for weight management: Assess your options carefully

**BY CAROLYN NEWBERRY, MD**

Considering the continued rise in obesity rates in this country coupled with an increase in associated digestive disease burden from conditions such as nonalcoholic fatty liver disease (NAFLD), gastroesophageal reflux disease (GERD), and select gastrointestinal malignancies, I believe it is now more important than ever for gastroenterologists to familiarize themselves with weight-management principles and incorporate them into clinical practice. A growing arsenal of tools is available for addressing excess weight, including medications and novel endobariatric techniques. Although the latter are an important consideration in patients with obesity, lifestyle counseling with or without weight-loss medications sets the stage for sustainable weight-loss success and may eliminate the need for procedural intervention. As such, current guidelines set forth by multiple societies, including the American Gastroenterological Association, emphasize the importance of lifestyle counseling targeting caloric restriction and increased physical activity along with medical augmentation via pharmacological agents in eligible patients.


Dr. Newberry

Newer pharmacological agents are now approaching total-body weight-loss percentages of currently available endobariatric techniques while still showing high tolerance rates and long-term efficacy, indicating some patients who previously would require procedures to meet weight loss goals may no longer need them. Alternatively, these medications may augment efforts prior to procedures, enhancing overall total-body weight loss achieved. If patients are not introduced to such options initially and as a part of comprehensive care management planning, they may not achieve the same degree of weight-loss success and metabolic optimization.

*Dr. Newberry is with the Innovative Center for Health and Nutrition in Gastroenterology (ICHANGE), division of gastroenterology, Weill Cornell Medical Center, New York. She disclosed receiving speaker honoraria from Baxter International and InBody USA.*

**Read more!**

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

# Research Awards Program

Each year, the AGA Research Foundation provides research funding to transform the lives of talented investigators.

What will the practice of gastroenterology look like in 20 years? It is our hope that physicians have an abundance of new tools and treatments to care for their patients suffering from digestive disorders.

How will we get there? New treatments and devices are the result of years of research.

**AGA has made a commitment to support investigators in GI and hepatology with its Research Awards Program.**

To help make this dream a reality, AGA – through the AGA Research Foundation – has made a commitment to support investigators in GI and hepatology with its Research Awards Program. In the past year, the AGA Research Foundation provided $2.5 million in research funding to 61 highly qualified investigators. These diverse researchers range from young investigators to more seasoned leaders in GI, all embarking on novel research projects that will advance our understanding of digestive conditions and pave the way for future discoveries in the field.

The AGA Research Foundation sincerely thanks all of its donors – without their contributions, this work wouldn't be possible.

You can help spark the scientific breakthroughs of today so clinicians will have the tools to improve care tomorrow. Donate your tax-deductible gift today at www.gastro.org/donateonline. ■

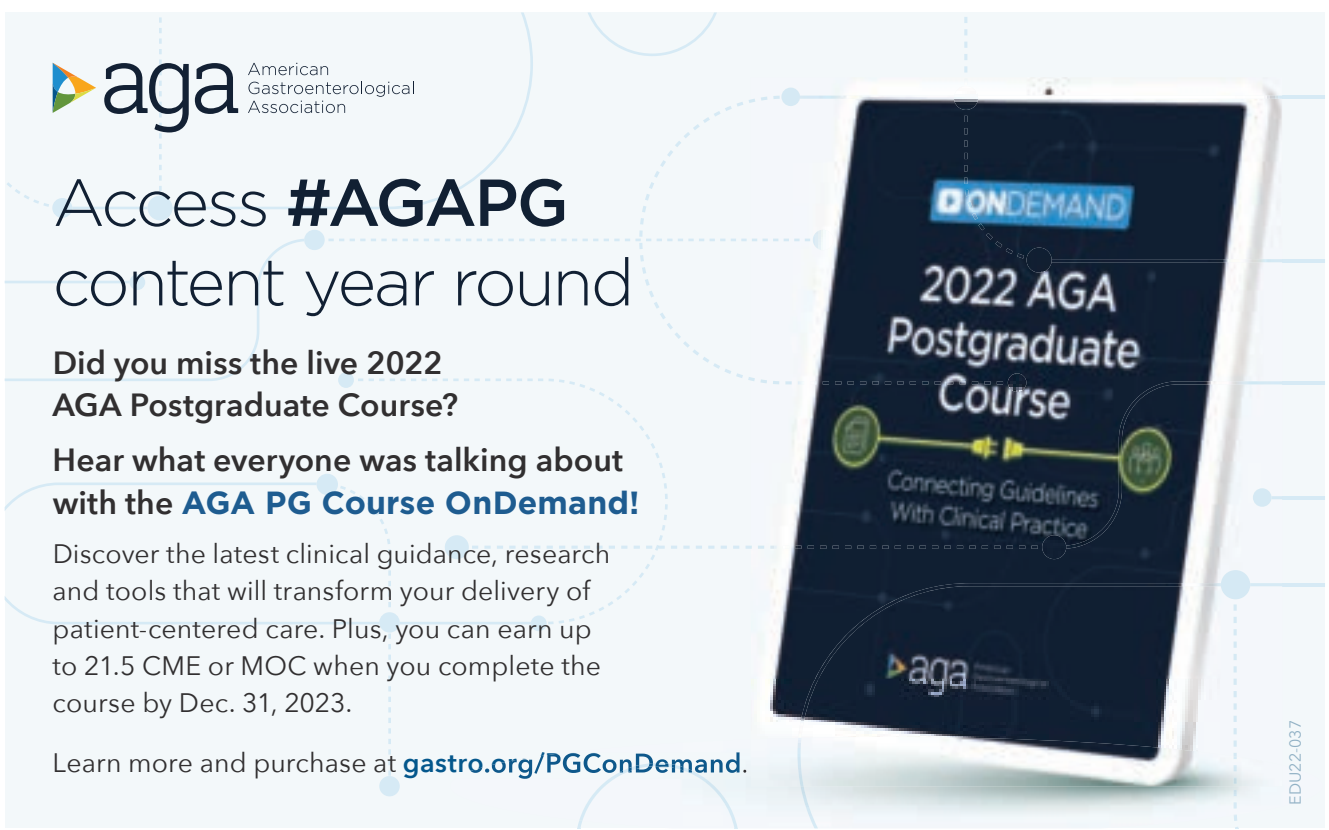
Courtesy AGA Institute

Previous recipients of the AGA Research Foundation's awards are shown.

# AGA makes its first investment through new GI innovation fund

AGA has announced that the association's new venture capital fund, GI Opportunity Fund 1, completed its first investment, rounding out the Series A financing of Virgo Surgical Video Solutions ("Virgo") of Carlsbad, Calif.

Virgo provides gastroenterologists, clinical trial sponsors, and trial site investigators with artificial intelligence–fueled, always-on endoscopic procedure recording and patient recruitment tools for clinical trials in gastroenterology, starting with inflammatory bowel disease clinical trials. ■

# IBD and pregnancy: What to tell your patients


Dr. Mahadevan


Dr. Dubinsky


Dr. Kane

While many gastroenterologists may be comfortable with inflammatory bowel disease, most are not experts in women's concerns about pregnancy. One study found that, although women with IBD may have concerns about the interplay of their disease and reproductive health, many have not had extensive conversations with their gastroenterologist about it (Crohns Colitis 360. 2021 Dec 29. doi: 10.1093/crocol/otab083). In fact, that same study found most women expect their gastroenterologist to initiate these conversations.

GI & Hepatology News sought input from a patient advocate about questions women with IBD often think about but may not always discuss with their gastroenterologists, and then solicited responses from thought leaders in IBD and pregnancy. In this roundtable discussion, Uma Mahadevan, AGAF, MD, professor of medicine and the director of the Colitis and Crohn's Disease Center at the University of California, San Francisco; Marla C. Dubinsky, MD, professor of medicine at the Icahn School of Medicine at Mount Sinai, New York; and Sunanda V. Kane, AGAF, MD, professor of medicine at Mayo Clinic in Rochester, Minn., share how they respond to these questions in their clinical practice.

**"Uncontrolled inflammation is a key risk factor for spontaneous abortion in the first trimester. Medication we would use in pregnancy is not putting them at risk for spontaneous abortion or congenital anomalies."**

***What should a woman with IBD who is interested in having biological children in the future be thinking about now?***

**Dr. Mahadevan:** Because active disease is associated with lower rates of conception and higher rates of pregnancy loss, women with IBD should first ensure they are in remission. I like to document endoscopic healing with a colonoscopy or sigmoidoscopy, but, if this has been done recently, a fecal calprotectin test can be helpful.

Women with IBD, particularly those with small-bowel disease, are at risk for nutritional deficiencies, so prior to conception, I also check vitamin $B_{12}$, vitamin D, and iron, and repeat as needed. Zinc and folate can be considered. Those who are underweight should work with a nutritionist to ensure adequate caloric intake.

**Dr. Dubinsky:** I think it's also important to stress the importance of taking their IBD medications because they can help patients achieve and maintain disease remission. Uncontrolled inflammation is a key risk factor for spontaneous abortion in the first trimester. Medication we would use in pregnancy is not putting them at risk for spontaneous abortion or congenital anomalies, which is what mothers to be are understandably most concerned about.

I am very honest and transparent with my patients: "About the only thing I need to take care of is you. If you are good, the baby is good."

**Dr. Kane:** As Dr. Mahadevan mentioned, women with IBD are at higher risk for vitamin deficiencies so those need to be corrected before conception. If they smoke, they should stop before conceiving.

There is no increased risk of infertility unless there has been a history of abdominal surgery.

Also, if women are not actively planning on getting pregnant, that would be important to share because some gastroenterologists will avoid certain effective medications if pregnancy is a possibility.

***If a woman has had surgery for her IBD, could that make it harder for her to get pregnant?***

**Dr. Kane:** Yes, it can because scar tissue may develop within the pelvis. However, if surgery is indicated to manage a patient's IBD, then talk to the surgeon about ways that they might be able to reduce the risk of scar tissue formation.

**Dr. Dubinsky:** One thing to note is that almost all the data on infertility risk and scarring are based on open surgical techniques that involve dissection of the rectum. On the other hand, we don't yet have enough prospective data on the impact of the modern era of laparoscopic surgery to suggest whether it affects fertility. More data are needed because providers may be giving women old information that is no longer relevant in the modern era.

***If a woman is experiencing IBD symptoms, should she attempt to conceive?***

**Dr. Kane:** Gastrointestinal symptoms in patients with IBD could be from active disease but also other things, so it's important to have a thorough check-up to assess if there is active disease or not. Active disease can (but does not always) lead to a more complicated pregnancy, and conception is not recommended while a patient has active IBD.

**Dr. Dubinsky:** Although some patients feel an urgency to conceive regardless of disease activity, we need to do our due diligence and explain that we need to focus on getting them into the deepest remission possible, including endoscopic findings, biomarkers, and symptoms.

The most important gift you can give your future moms is to optimize the therapy they're on before they conceive.

***Is it important for someone who's working with a gastroenterologist and an obstetrician to also work with a maternal-fetal medicine (MFM) specialist?***

**Dr. Kane:** Having a diagnosis of IBD makes a woman's pregnancy "high risk" because just having the diagnosis is associated with a higher risk of prematurity and small for gestational age – but importantly, not birth defects. A woman whose IBD is in remission should still have a discussion with an MFM specialist, just so everyone is on the same page.

**Dr. Dubinsky:** I refer to care with MFM specialists as "tighter monitoring." I tell my patients that MFM specialists have managed many complex pregnancies and feel confident around the safety of their medications, understand the impact of when the baby may be exposed to certain medications, and will focus on following them more closely.

***What are the risks of IBD medications during pregnancy and while breastfeeding? Should women stop their medications during pregnancy and breastfeeding?***

**Dr. Dubinsky:** Organogenesis occurs in the first 10 weeks, so any medicines that cross the placenta during that time are up for discussion and debate. Methotrexate and the newer small molecules, such as Janus kinase (JAK) inhibitors and S1P receptor modulators, do cross the placenta during the first trimester and need to be discontinued before conception, sometimes as early as 3 months before conception.

However, biologics are very large proteins and do not cross the placenta until closer to week 27. We are not advocating stopping biologics in advance of conception, or during pregnancy, or during breastfeeding. There is more risk to stopping than continuing.

**Dr. Mahadevan:** Methotrexate should be stopped at least 3 months prior to conception and should not be taken during pregnancy.

There are limited antibiotic safety data in pregnancy for the longer periods of time used in IBD. I generally prefer amoxicillin/clavulanic acid over ciprofloxacin or metronidazole, but short-term (less than

2 weeks) use of any of those three are not contraindicated.

Mesalamine agents and thiopurine monotherapy can be continued through pregnancy and breastfeeding.

Biologic agents, such as anti–tumor necrosis factor, anti-interleukin 23, anti-integrin, and biosimilars, can be continued through pregnancy and during breastfeeding. Given limited exposure in the first trimester, there is no evidence of increased risk of birth defects. As Dr. Dubinsky pointed out, there is active transfer, particularly in the third trimester and minimal transfer in breast milk, but this has not been associated with harm.

Lastly, small molecules, such as the JAK inhibitors tofacitinib and upadacitinib, as well as ozanimod, have virtually no human safety data during pregnancy, and animal data show harm. The use of these agents in pregnancy is not recommended.

**For ulcerative colitis, mode of delivery is based on obstetric, not gastrointestinal, variables. For Crohn's disease, if there is evidence of perianal disease, then a cesarean is appropriate.**

**Dr. Kane:** As Dr. Dubinsky stated, most of the medications our patients take are low risk to continue through pregnancy if the patients are in remission. Although a woman "in remission" on steroids is not really in remission and should not get pregnant until she is on something else.

As far as breastfeeding goes, that should be stopped if the patient is on methotrexate, cyclosporine, or certain antibiotics. If she is on more than 20 mg of prednisone this can pass to the infant, and a mother should not breastfeed.

Women should avoid fenugreek as a lactation aid, as that contains a compound that can promote bleeding. Lactation cookies are ok.

Otherwise, there are lots of potential benefits to breastfeeding, and I encourage it.

***How is a flare treated if it occurs during pregnancy?***

**Dr. Dubinsky:** A flare during pregnancy is treated the same as a flare outside of pregnancy. We want to use noninvasive ways to confirm it, but I think we don't need to overly investigate in most of our women. If they're already on a biologic, you may consider changing.

Some women may need corticosteroids. It's not our favorite move, but there is an urgency to getting a flare under control during pregnancy because of possible complications.

**Dr. Mahadevan:** Some of this is contingent on when during pregnancy the flare occurs. A patient who has a flare at 38 weeks' gestation will likely proceed with delivery and the flare will be dealt with separately. Someone at 8 weeks' gestation is at high risk for pregnancy loss, so treatment should be quick and effective.

As does Dr. Dubinsky, I do try to avoid steroids if possible. For example, I would rather start an effective biologic right away than drag out steroids to see if they will respond.

**Dr. Kane:** I would add that, if a mother is losing weight, she might need to be hospitalized for additional nutritional support. If surgery is necessary, we usually try to time it for the second or third trimester.

What needs to be taken into consideration regarding mode of delivery? Also, if a woman has undergone prior surgeries, do they increase the risk of delivery complications?

For ulcerative colitis, mode of delivery is based on obstetric, not gastrointestinal, variables. For Crohn's disease, if there is evidence of perianal disease, then a cesarean is appropriate. If there is no history of perianal disease, then delivery is based on obstetric variables.

For a woman who has a J pouch, if possible, the surgeon who created it should be contacted to ask about the technical aspects of the pouch and how it lies in the pelvis.

***What's the risk of a postpartum flare if a woman's IBD remains in clinical remission during pregnancy?***

**Dr. Mahadevan:** There is no increased risk of postpartum flare if a woman continues her IBD medications after delivery. Many of the reports of flare are from stopping medications (mistakenly often) to breastfeed.

**Dr. Kane:** As Dr. Mahadevan said, the risk of a flare is usually because a woman stops taking her medications because she thinks that medication will be passed to the infant through breastfeeding, which in most cases is not true.

ZORANM/GETTY IMAGES

Otherwise, there is not an increased risk of a flare in a 12-month period. However, it is important to monitor for symptoms after delivery; the risk of a flare is not zero.

***What symptoms should women watch out for after delivery that may indicate an uptick in disease activity?***

**Dr. Kane:** The same symptoms as before they were pregnant. Diarrhea, abdominal pain, and rectal bleeding are not normal after delivery and should be considered signs of returning disease.

***As a gastroenterologist, is there any additional advice you'd offer about conception, fertility, and pregnancy when treating women with IBD?***

**Dr. Mahadevan:** Women with IBD should, when feasible, have a planned pregnancy when in documented remission and under the care of their gastroenterologists, obstetrician, and an MFM specialist. Life happens, and this is not always possible. That said, a woman with IBD has the same chance of getting pregnant as a woman of the same age without IBD, unless she has active disease or a history of pelvic surgery. Women with IBD in remission will generally have healthy pregnancies if they continue appropriate medications.

**Dr. Kane:** Agreed. The majority of women with IBD will have normal, healthy pregnancies. It is important for them to not stop their IBD therapy without talking to their gastroenterologist first. Well-intentioned but ignorant obstetricians or midwives may recommend stopping, but then panic when disease flares and the mother's health is at risk. Active inflammation is the worst enemy to a pregnancy, not active therapy.

**Dr. Dubinsky:** One additional thing to consider is: How do we help women with IBD who have delivered meet the needs of their family and continue to stay on their meds and be in good inflammatory control?

For example, we can give the biologic in the hospital after they've had a cesarean or a vaginal delivery and before they leave. We know that that is safe, giving that to them before they leave the hospital is a huge value added.

Another thing is possibly changing their infusions to home infusions. That would be helpful for the moms as well. ■

*Dr. Mahadevan reports being a consultant for AbbVie, Janssen, Pfizer, Gilead, Bristol-Myers Squibb, Takeda, Protagonist, Prometheus, and Boehringer Ingelheim. Dr. Dubinsky is a consultant for AbbVie, Arena, Bristol-Myers Squibb, Janssen, Eli Lilly, Takeda, and Prometheus BioSciences. She is a shareholder and CEO of a publicly traded company, Trellis Health. Dr. Kane is a consultant for Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Janssen, Takeda, Seres Therapeutics, TechLab, United Healthcare, Predicta-Med, and InveniAI, and is the editor for the IBD section of UptoDate.*

**AGA Resource**

Planning for a family can be challenging, and if your patient has IBD, there are additional factors to consider. The AGA IBD Parenthood Project (https://ibdparenthoodproject.gastro.org) is the "go-to" resource for everything patients need to know about IBD and pregnancy throughout all stages of family planning.

# Don't wait for patients to bring up their GI symptoms

BY CAROLYN CRIST
*MDedge News*

Nearly three-quarters of Americans would wait before discussing GI symptoms with a health care provider if their bowel frequency or symptoms changed, with more than a quarter waiting for symptoms to become severe, according to an American Gastroenterological Association survey.

Nearly 40% of people said GI symptoms had disrupted everyday activities such as exercising, running errands, and spending time with family or friends, but despite these disruptions, 30% of people said they would discuss their bowel-related concerns only if their doctor brought it up first. In response, the AGA launched "Trust Your Gut," an awareness campaign aimed at shortening the time from the onset of bowel symptoms to discussions with health care providers.

"So many patients are either fearful or embarrassed about discussing their digestive symptoms such that they delay care unless the health care provider brings it up," said Rajeev Jain, MD, AGAF, a gastroenterologist with Texas Digestive Disease Consultants, AGA patient education adviser and a Trust Your Gut spokesperson.

"This potential delay could be detrimental in some cases, such as bleeding related to colon cancer," he said. "If diagnosed sooner, an operation or chemotherapy could lead to treatment and a cure in those cases, versus advanced cancer that may be incurable."

The AGA Trust Your Gut survey, conducted by Kelton Global during May 9-11, 2022, included 1,010 respondents from a nationally representative sample of U.S. adults.

### Struggling with the issue

About 28% of respondents said they would see a clinician immediately if their bowel frequency or symptoms changed. However, 72% said they would wait, and on top of that, 27% said they would wait until the condition became severe or didn't resolve over time. Women were more likely than men to say they would wait, at 72% versus 64%.

**Many respondents were raised to avoid the topic of bowel issues. About 23% said their parents encouraged them not to mention bathroom-related health issues.**

Overall, 39% of respondents said bowel issues have stopped them from doing some type of activity in the past year. Men were more likely than women to say that bowel issues have affected their ability to do an activity, at 44% versus 35%.

"Typically, when it comes to functional or motility disorders or bowel dysfunction, we tend to see a higher prevalence in women, so this was somewhat surprising to see," said Andrea Shin, MD, a gastroenterology specialist and assistant professor of medicine at Indiana University, Indianapolis, and AGA patient education adviser designate.

**AGA resource**
Help your patients learn more by encouraging them to visit https://patient.gastro.org/trust-your-gut/.

"Part of this difference may be related to the communication barrier and how sex or gender affects that relationship between a clinician and a patient," she said.

The reasons vary, but themes of uncertainty and embarrassment are prevalent. About 33% said they're not sure whether the symptoms are a problem, 31% said they hope the symptoms improve on their own, 23% said it's embarrassing, and 12% don't know what to tell the doctor. Men were more likely than women to say they don't know what to say to a doctor about their symptoms, at 15% versus 9%.

### Starting the conversation

Many respondents were raised to avoid the topic of bowel issues. About 23% said their parents encouraged them not to mention bathroom-related health issues, and 10% said they didn't talk about bowel issues at all; 32% said they had to use code words, such as "go to the bathroom" or "potty."

"What this highlights is that patients are culturally taught not to talk about their digestive tract, or they're embarrassed or uncertain," Dr. Jain said. "At the end of the day, we need to destigmatize discussions about digestive function and normalize it as part of overall health."

Survey respondents said they'd feel most comfortable talking about bowel issues with doctors (63%) and nurses (41%), as well as a significant other (44%), parent (32%), or friend (27%). Women were more likely than men to feel comfortable turning to a nurse practitioner or physician's assistant (47% versus 35%) or friend (30% versus 24%).

To feel more comfortable with these conversations, 42% of survey participants said they would like their doctor or clinician to describe what's normal. About 30% want to know the appropriate terms to describe their situation. Health care providers should also consider cultural and social factors that may affect a patient's disease experience, as well as how they interact with the health care system, Shin said.

"Understanding these differences might help us to better engage with a community that is diverse. In general, we also need to be more proactive about drawing these conversations out of patients, who may not mention it unless we ask because they find it so personal."

The AGA Trust Your Gut campaign is supported by a sponsorship from Janssen. Dr. Jain and Dr. Shin reported no relevant disclosures.

DDSEP10
Digestive Diseases Self-Education Program

## Quick quiz answers

*Questions on page 8.*

**Q1. Correct answer:**
**D. Rabeprazole**
**Rationale**
Within-class switching of proton pump inhibitors (PPIs) for patients with incomplete control of symptoms is frequently done in clinical practice. For the management of gastroesophageal reflux disease, this practice can be "considered" according to guidelines. More recent data suggest varying potencies of PPIs might be responsible for some patient's incomplete response. When measured as omeprazole equivalents, the relative potencies of standard-dose pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole have been estimated at 0.23, 0.90, 1.00, 1.60, and 1.82 OEs, respectively.

**References**
Graham DY and Tansel A. Clin Gastroenterol Hepatol. 2018;16(6):800-8.e7. doi: 10.1016/j.cgh.2017.09.033.

Katz PO et al. Am J Gastroenterol. 2022;117(1):27-56. doi: 10.14309/ ajg.0000000000001538.

Kirchheiner J et al. Eur J Clin Pharmacol. 2009;65(1):19-31. doi: 10.1007/s00228-008-0576-5.

**Q2. Correct answer:**
**A. Enteric infection**
**Rationale**
Despite the numerous side effects associated with long-term PPI use, the quality of evidence and risk of confounding from these studies limits the ability to ascribe sufficient cause and effect between PPI use and these outcomes. However, a recent large randomized controlled trial that evaluated the use of pantoprazole versus placebo demonstrated a statistically significant difference between the pantoprazole and placebo groups only in enteric infections (1.4% vs 1.0%; odds ratio, 1.33; 95% confidence interval, 1.01-1.75). Despite a nearly double increased risk of *Clostridioides difficile* infection in the PPI group, compared with the placebo group, the number of events was low, and the difference did not reach statistical significance. In the context of these data, and more recent studies suggesting an increased risk of COVID-19 in patients who take PPIs, compared with those who do not, the risk of enteric infections is likely small but significantly increased among long-term PPI users.

**References**
Freedberg DE et al. Gastroenterology. 2017;152(4):706-15. doi: 10.1053/j.gastro.2017.01.031.

Moayyedi P et al. Gastroenterology. 2019;157(3):682-91.e2. doi: 10.1053/j.gastro.2019.05.056.

# Downward trend in Medicare payments for GI services

**FROM STAFF REPORTS**

There has been a steady decline in Medicare reimbursement for common gastrointestinal services and patient office visits over the past 15 years, which could have a direct impact on patients.

"When Medicare reimbursements decrease, health outcomes, health care access, and patient satisfaction may be affected, particularly in light of high inflation and increased costs due to staffing shortages, increased staffing salaries, and additional equipment necessary for COVID-19 safety," researchers wrote in the American Journal of Gastroenterology (2022 Oct 28. doi: 10.14309/ajg.0000000000002010).

Samir A. Shah, MD, AGAF, of Brown University, Providence, R.I., and colleagues evaluated trends from 2007 to 2022 in Medicare reimbursement for the top 10 common GI procedures.

These procedures, which included colonoscopies, endoscopies, and gastrostomy tube placement, were identified through a joint list published by the American College of Gastroenterology, the American Society of Gastrointestinal Endoscopy, and the American Gastroenterological Association.

From 2007 to 2022, unadjusted and adjusted reimbursement for GI procedures declined by 7% and 33%, respectively, on average.

The adjusted change in reimbursement ranged from a decrease of roughly 29% for esophagus endoscopy to 38% for colonoscopy and biopsy, the study team found. They found that the decline in reimbursement of GI procedures was significantly larger after 2015 ($P < .001$).

From 2007 to 2014, the mean decrease in physician reimbursement for GI services was 6.7%, and the annual growth rate in reimbursement was –1.0%. In comparison, from 2015 to 2022, the mean decrease in physician reimbursement was 28.2%, and the mean annual growth rate in reimbursement was –4.7%.

To examine trends in reimbursement for office and inpatient visits from 2007 to 2022, the researchers identified the top five current procedural terminology (CPT) codes from outpatient office and inpatient consult visits provided to Medicare Part B beneficiaries by gastroenterologists.

In contrast to the reimbursement trends for GI procedures, the unadjusted physician reimbursement for inpatient and outpatient visits showed an average increase of 32%. However, after adjustment for inflation, physician reimbursement for patient visits showed an average decline of 4.9%. Overall, reimbursement for outpatient visits increased by 4.3%, while reimbursement for inpatient visits decreased by 18.8%.

Physicians once again faced cuts of at least 4.5% on Jan. 1. AGA and the entire medical community continue to call on Congress to make statutory changes to the Medicare payment system to address these payment challenges. Specifically, AGA and the physician community have recommended that payment rates include an inflationary adjustment similar to what other providers, such as hospitals, nursing homes, and ambulatory surgery centers, receive to account for practice, equipment, labor, and other costs associated with running a clinical practice.

AGA continues to urge physicians to write federal lawmakers to educate Congress about the detrimental effects of payment cuts, noting that the cuts, when coupled with rising inflation, increased administrative burdens, and staffing shortages, will negatively impact access to care.

The study had no financial support. The authors disclosed they have no conflicts. ■

# CLASSIFIEDS

## PROFESSIONAL OPPORTUNITIES

# Terlipressin decreases need for renal replacement therapy in liver transplant recipients

**BY CAROLYN CRIST**
*MDedge News*

In a subgroup of patients with hepatorenal syndrome (HRS) type 1 who received a liver transplant, terlipressin treatment appears to reduce the need for renal replacement therapy (RRT) through 12 months of follow-up, according to a study presented at the annual meeting of the American College of Gastroenterology.

Among transplant recipients, overall 12-month survival was 11% higher for those treated with terlipressin compared with placebo, said K. Rajender Reddy, MD, director of hepatology and medical director of liver transplantation at the University of Pennsylvania, Philadelphia.

"Hepatorenal syndrome type 1 is a potentially reversible form of acute kidney injury that occurs in the setting of end-stage liver disease," he said.

Liver transplantation, which eliminates end-stage liver disease, is the only definitive treatment for HRS. However, renal replacement therapy is common and associated with poor clinical outcomes and low patient survival rates in both the pretransplant and posttransplant settings, he noted.

**Renal replacement therapy is common and associated with poor clinical outcomes and low patient survival rates in both the pretransplant and posttransplant settings.**

Terlipressin, an injectable synthetic vasopressin analogue, restores renal blood flow and reverses HRS in 20%-40% of patients, Dr. Reddy said. In September 2022, the U.S. Food and Drug Administration approved terlipressin (Terlivaz) for patients with HRS type 1. The label has a boxed warning for serious or fatal respiratory failure.

The safety and efficacy were assessed in the phase 3 CONFIRM trial, which Dr. Reddy and colleagues previously published (N Engl J Med. 2021 Mar 4. doi: 10.1056/NEJMoa2008290). The randomized, placebo-controlled study demonstrated that terlipressin reversed HRS and reduced the need for RRT through day 30. The reversal of HRS with terlipressin did not improve 90-day survival as compared with placebo, which researchers attributed to a higher death rate within 90 days after the first dose despite improved kidney function.

### A closer look at the liver transplant patients

In the subgroup analysis of the CONFIRM study, Dr. Reddy and colleagues analyzed the clinical outcomes through 12 months of follow-up in patients with HRS who received a liver transplant. They looked at the incidence of verified HRS reversal, HRS reversal, need for RRT, and overall survival.

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Verified HRS reversal was defined as two consecutive serum creatinine measurements of 1.5 mg/dL or less at least 2 hours apart up to day 14 and survival without RRT for at least 10 days. HRS reversal was defined as a serum creatinine level of 1.5 mg/dL or less while on treatment. In addition, the need for RRT and overall survival were assessed at days 30, 60, 90, 180, and 365.

RRT was defined as any procedure that replaced nonendocrine kidney function, including continuous hemofiltration and hemodialysis, intermittent hemodialysis, peritoneal dialysis, ultrafiltration, or other dialysis and filtration techniques.

**"Collectively, these data indicate that terlipressin treatment in patients with HRS led to better long-term clinical outcomes in those who received a liver transplant."**

In the CONFIRM study, 199 patients with HRS were treated with terlipressin plus albumin, and 101 patients were treated with placebo plus albumin for up to 14 days. In the terlipressin group, 46 patients received liver transplants within the first 2 months of the study, as did 29 in the placebo group. Two patients in the terlipressin group and one in the placebo group received a simultaneous liver-kidney transplant.

### Meaningful clinical outcomes

In the 12-month follow-up subgroup analysis, verified HRS reversal was statistically comparable between the groups, with a 30% decrease in the terlipressin group and 17% decrease in the placebo group, Dr. Reddy reported.

HRS reversal was higher in the terlipressin group, at 37%, as compared with 14% in the placebo group.

The pretransplant need for RRT was lower in the terlipressin group, at 30%, as compared with 62% in the placebo group. The posttransplant need for RRT remained numerically lower in the terlipressin group at all time points and was significantly lower at day 180 and day 365.

Overall survival for transplant recipients in the terlipressin group was 94%, as compared with 83% in the placebo group. Posttreatment adverse events and severe adverse events were similar between the groups.

"Collectively, these data indicate that terlipressin treatment in patients with HRS led to better long-term clinical outcomes in those who received a liver transplant," Dr. Reddy said.

The study was funded by Mallinckrodt Pharmaceuticals, which manufactures terlipressin. One author is an employee of Mallinckrodt, and the other authors have served in an advisory role or received grant support from Mallinckrodt. The authors also disclosed consultant roles and research support from several other pharmaceutical companies. ■

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