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The study underscores the importance of "early messaging" about screening as patients approach age 45, investigators said.

Registry data support lowering CRC screening age

BY BRANDON MAY
MDedge News

Approximately one-third of people between 45 and 49 years of age who undergo colonoscopies have neoplastic colorectal pathology, according to a retrospective analysis.

According to the researchers, led by Parth Trivedi, MD, of the Icahn School of Medicine at Mount Sinai, New York, there has progressively been a "disturbing" rise in early-onset colorectal cancer (CRC) in the United States, which has prompted guidelines from the American Cancer Society to the U.S. Preventive Services Task Force to recommend lowering the CRC screening starting age to 45 years old for average-risk individuals. Despite these recommendations, little research to date has fully characterized the prevalence of colorectal neoplasia in individuals younger than the currently recommended CRC onset screening age of 50 years.

Dr. Trivedi and colleagues, who published their study

See **CRC** *page 9*

Artificial intelligence aids assessment of UC activity, remission

BY SARA FREEMAN
MDedge News

Not only are artificial intelligence (AI) systems potentially highly accurate for assessment of disease activity and remission of ulcerative colitis (UC), but they can mitigate some limits of human assessment, according to presentations at the 17th congress of the European Crohn's and Colitis Organisation.

Importantly, AI systems have the potential to supplement the services of expert histopathologists and endoscopists rather than replace them, several experts asserted at the meeting.

"We will always need pathologists," reassured inflammatory bowel disease (IBD) specialist Laurent Peyrin-Biroulet, MD, PhD, of Nancy (France) University Hospital, who presented about the use of an AI-driven scoring system to measure histological disease activity in UC.

Dr. Peyrin-Biroulet, who is the president of ECCO and acts as the scientific secretary of the International Organization for the Study of IBD, added that the use of AI systems could mean that pathologists have more time to do other tasks. Not only that, but it's also not always possible to have an IBD pathologist in every center, everywhere in the

See **Assessment** · *page 41*

Novel scoring system emerges for alcoholic hepatitis mortality risk

BY MARCIA FRELLICK

A new scoring system proved more accurate than several other available models at predicting the 30-day mortality risk for patients with alcohol-associated hepatitis (AH), according to new data.

The system, called the Mortality Index for Alcohol-Associated Hepatitis (MIAAH), was created by a team of Mayo Clinic researchers, who published their results in Mayo Clinic Proceedings (2022 Feb 15. doi: 10.1016/j.mayocp.2021.10.026).

Among the currently available prognostic

See **Scoring system** · *page 20*

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LETTER FROM THE EDITOR

Celebrating our colleagues

In this month's issue of GI & Hepatology News, we celebrate the recently named recipients of this year's AGA Recognition Prizes, several of whom I am privileged to work with on a daily basis. We also welcome the newest members of AGA's Governing Board, who are outstanding leaders and representative of a much larger group of volunteer members who work tirelessly to advance AGA's initiatives to enhance the clinical practice of gastroenterology and improve patient outcomes.

Dr. Adams

The Governing Board represents "a much larger group of volunteer members who work tirelessly to advance AGA's initiatives to enhance the clinical practice of gastroenterology and improve patient outcomes."

This month's issue also highlights two newly-developed clinical risk-prediction tools – one designed to assist clinicians in predicting alcoholic hepatitis mortality, and another designed to identify inflammatory bowel disease (IBD) patients at high-risk of developing venous thromboembolism (VTE) post hospitalization. While no prediction model is perfect, these tools can positively impact clinical decisionmaking and contribute to improved patient outcomes. We also include recommendations on managing IBD in older patients, and report on a study suggesting an increase in late-stage cancer diagnoses in the wake of the COVID-19 pandemic. AGA's new clinical guideline on systemic therapy for hepatocellular carcinoma and Clinical Practice Update on non invasive colorectal cancer screening also are featured. Finally, in this month's Practice Management Toolbox, Dr. Feuerstein, Dr. Sofia, Dr. Guha, and Dr. Streett offer timely recommendations regarding how to overcome existing barriers to achieve high-value IBD care.

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

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GI&Hepatology News

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Cryoballoon ablation demonstrates long-term durability in Barrett's esophagus

BY BRANDON MAY
MDedge News

Similar to radiofrequency ablation, cryoballoon ablation (CBA) is a durable approach that can eradicate Barrett's esophagus in treatment-naive patients with dysplastic BE, according to a single-center cohort study.

Endoscopic mucosal resection (EMR), radiofrequency ablation (RFA), and cryotherapy are established techniques used in endoscopic eradication therapy of BE, wrote study authors led by Mohamad Dbouk, MD, of Johns Hopkins Medical Institutions in Baltimore in Techniques and Innovations in Gastrointestinal Endoscopy (2021 Nov 30. doi: 10.1016/j.tige.2021.11.007). Unlike RFA which uses heat to induce tissue necrosis and reepithelialization of normal tissue, cryotherapy applies extreme cold in the treatment of BE. While cryotherapy as an endoscopic ablative technique has been studied over the past decade as an alternative treatment modality, Dr. Dbouk and researchers noted that long-term data on durability of response and outcomes with this approach are lacking.

While cryotherapy as an endoscopic ablative technique has been studied over the past decade, long-term data on durability of response and outcomes with this approach are lacking.

To gauge the durability of CBA for dysplastic BE, the researchers examined outcomes of 59 consecutive patients with BE and confirmed low-grade dysplasia (n = 22), high-grade dysplasia (n = 33), or intramucosal cancer (n = 4), all of whom were treated with CBA for the purposes of BE eradication. The single-center cohort comprised only treatment-naive patients who had a mean age of 66.8 (91.5% male). In the overall cohort, the mean length of the BE was 5 cm, although 23.7% of patients had BE ≥8 cm in length.

Following confirmation of dysplastic BE in biopsies and/or EMR specimens at baseline, patients underwent CBA applied to the gastric cardia as well as all visible BE with the cryoballoon focal ablation system and focal or pear-shaped cryoballoon. The investigators performed surveillance esophagogastroduodenoscopy (EGD) to assess the CBA response. Patients with high-grade dysplasia underwent EGD and biopsy every 3 months for the first year after completing CBA, every 6 months for the second year, and once per year thereafter. However, those with biopsies at baseline that showed low-grade dysplasia (LGD) underwent EGD and biopsy every 6 months during the first year after CBA and annually thereafter. Retreatment with ablation was allowed if recurrent dysplasia or intestinal metaplasia was found.

The study's primary endpoints included short-term efficacy – defined as the rate of complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM) at 1-year follow-up – and durability – characterized by the proportion of patients with CE-D and CE-IM within 18 months and maintained at 2- and 3-year follow-up.

The median follow-up period for the patient cohort was 54.3 months. Approximately 95% of the 56 patients who were evaluable at 1 year achieved CE-D, while 75% achieved CE-IM. In an analysis that stratified patients by their baseline dysplasia grade, the rates of CE-D were each 96% in the LGD and HGD groups. At 1 year, the median number of CBA sessions used to achieve CE-IM was 3.

Throughout treatment and the follow-up period, none of the patients progressed beyond their dysplasia grade at baseline or developed esophageal cancer. All patients had maintained CE-D for years 2, 3, and 4. In addition, 98% of patients had CE-IM at 2 years, 98% had CE-IM at 3 years, and 97% of patients had CE-IM at 4 years. After stratification of patients by baseline grade of dysplasia, the researchers found no significant difference between groups in the rates of CE-D and CE-IM at each follow-up year.

In 48 patients who initially achieved CE-IM, 14.6% developed recurrent intestinal metaplasia (IM), including six in the esophagus and one in the GEJ, after a median of 20.7 months. Approximately 57% of patients who developed recurrent IM had baseline LGD, while 43% had HGD at baseline. The length of BE was not significantly associated with the risk of IM recurrence, according to a Cox proportional hazard analysis (hazard ratio, 1.02; 95% confidence interval, 0.86-1.2; $P = .8$).

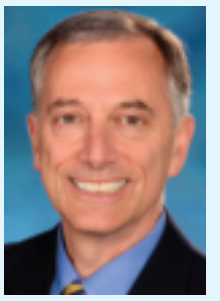
Approximately 8.5% of patients had post-CBA strictures that required dilation during the study period. According to bivariate analysis, individuals with a BE length of ≥8 cm were significantly more likely to develop strictures, compared with patients without ultra-long BE (28.6% vs. 2.2%, respectively; $P = .009$). Strictures occurred during the first 4 months after the initial CBA. The median period from the first CBA treatment to stricture detection on follow-up EGD was 2 months. Around 1.7% of patients experienced postprocedural bleeding that required clipping for closure. These patients were on clopidogrel for atrial fibrillation during the first year of active treatment.

Limitations of the study included the small sample size as well as the inclusion of patients from a single center, which the researchers suggest may limit the generalizability of the results.

"More research is needed to confirm the long-term durability of CBA," the authors concluded. "Randomized controlled trials comparing CBA with RFA are needed to assess the role of CBA as a first-line and rescue EET."

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

Barrett's endoscopic eradication therapy, resection of visible lesions, and ablation of remaining Barrett's mucosa are the standard of care for dysplasia management. Radiofrequency ablation (RFA) is 91% successful in eliminating dysplasia and 78% in eliminating intestinal metaplasia (IM). Recurrence of dysplasia is rare, although recurrence of IM is 20%.


Dr. Greenwald

This study by Dbouk et al. examines the success of a newer ablation modality, the cryoballoon focal ablation system (CbFAS), in ablating Barrett's tissue. With CbFAS, mucosa is focally ablated by freezing when in contact with a nitrous oxide–cooled balloon. In this single-center, single-operator study, CbFAS successfully eliminated dysplasia and IM for up to 4 years at rates comparable to RFA, with dysplasia and IM recurrence seen in 1.9% and 14.6%. The stricture rate was 8.5%, higher than the 5% typically reported for RFA.

Given the impressive results of RFA, one might ask why alternative ablation therapies are needed. CbFAS equipment costs are lower than those of RFA, and discomfort after the procedure may be less. Failure of ablation is poorly understood, likely attributable to inadequate reflux suppression and maybe thicker areas of Barrett's mucosa. The greater depth of injury with cryoablation may succeed in some cases of RFA failure. Complexity of this ablation procedure remains high, and excessive overlap of treatment sites probably explains the higher stricture rate. Where cryoballoon ablation fits in the Barrett's ablation paradigm is not clear. The lower cost and availability may provide traction for this new technology in the established field of Barrett's ablation.

Bruce D. Greenwald, MD, is a professor of medicine at the University of Maryland, Baltimore, and the Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore. He is a consultant for Steris Endoscopy.

Crohn's: Ultrasound tested as colonoscopy alternative

BY WILL PASS
MDedge News

Bowel ultrasound predicts the clinical course of Crohn's disease for up to 1 year, according to results of a prospective trial involving 225 patients.

After additional confirmation in larger studies, ultrasound could serve as a noninvasive alternative to colonoscopy for monitoring and predicting disease course, reported lead author Mariangela Allocca, MD, PhD, of Humanitas University, Milan, and colleagues.

"Frequent colonoscopies are expensive, invasive, and not well tolerated by patients, thus noninvasive tools for assessment and monitoring are strongly needed," the investigators wrote in Clinical Gastroenterology and Hepatology (2021 Apr 21. doi: 10.1016/j.cgh.2021.04.029). "Bowel ultrasound accurately detects inflammatory bowel disease activity, extent, and complications, particularly in Crohn's disease. Considering its low cost, minimal invasiveness ... and easy repeatability, bowel ultrasound may be a simple, readily available tool for assessing and monitoring Crohn's disease."

To test this hypothesis, Dr. Allocca and colleagues enrolled 225 consecutive patients with ileal and/or colonic Crohn's disease diagnosed for at least 6 months and managed at a tertiary hospital in Italy. All patients underwent both colonoscopy and bowel ultrasound with no more than 3 months between each procedure.

WACHARAPHORN PHETPRADUB/EYEEM/GETTY IMAGES

Colonoscopy results were characterized by the Simplified Endoscopic Score for Crohn's Disease (SES-CD), whereas ultrasound was scored using a several parameters, including bowel wall pattern, bowel thickness, bowel wall flow, presence of complications (abscess, fistula, stricture), and characteristics of mesenteric lymph nodes and tissue. Ultrasound scores were considered high if they exceeded a cut-off of 3.52, which was determined by a receiver operating characteristic curve analysis.

Participants were followed for 12 months after baseline ultrasound. The primary objective was to determine the relationship between baseline ultrasound findings and negative disease course, defined by steroid usage, need for surgery, need for hospitalization, and/or change in therapy. The secondary objective was to understand the relationship between ultrasound findings and endoscopy activity.

Multivariable analysis revealed that ultrasound scores greater than 3.52 predicted a negative clinical disease course for up to 1 year (odds ratio, 6.97; 95% confidence interval, 2.87-16.93; $P < .001$), as did the presence of at least one disease complication at baseline (OR, 3.90; 95% CI, 1.21-12.53; $P = 0.21$). A worse clinical course at 1 year was also predicted by a baseline fecal calprotectin value of at least 250 mcg/g (OR, 5.43; 95% CI, 2.25-13.11; $P < .001$) and male sex (OR, 2.60; 95% CI, 1.12-6.02; $P = .025$).

Investigators then assessed individual disease outcomes at 12 months and baseline results. For example, high ultrasound score and calprotectin at baseline each predicted the need for treatment escalation. In comparison, disease behavior (inflammatory, stricturing, penetrating) and C reactive protein predicted need for corticosteroids. The only significant predictor of hospitalization a year later was CRP.

"Frequent colonoscopies are expensive, invasive, and not well tolerated by patients, thus noninvasive tools for assessment and monitoring are strongly needed."

"[B]owel ultrasound is able to predict disease course in Crohn's disease patients," they wrote. "It may identify patients at high risk of a negative course to adopt effective strategies to prevent any disease progression. Our data need to be confirmed and validated in further large studies."

The investigators disclosed relationships with Janssen, AbbVie, Mundipharma, and others. ■

DDSEP 9
Digestive Diseases Self-Education Program

Quick Quiz

Q1. A 65-year-old male with no significant past medical history presents with significant diarrhea. He reports that for the past 3 months he has had four to five bowel movements a day. He characterizes them as greasy and foul smelling, but not entirely watery. He notices no blood or mucus in the stool. Over the same time period, he has also noticed increased swelling in both of his ankles. The physician sends a broad workup.

Stool testing results include the following:
- *Clostridioides difficile* – Negative.
- Stool Ova and Parasite – Negative.
- Stool Culture – Negative.
- Stool Elastase – Within normal limits.
- Fecal Fat (spot test) – Within normal limits.
- Stool Alpha-1 Antitrypsin – Elevated.

Which of the following diagnoses best explains the patient's symptoms?
A. Amyloidosis involving the small intestine.
B. Celiac disease.
C. Ulcerative Colitis.
D. Small-bowel dysmotility.

Q2. A 2-month-old male presents with abdominal distention and poor appetite. His family notes that the patient has chronic difficulties with constipation, reporting that they have to use a glycerin suppository to help him have a bowel movement every 2-3 days. The family reports that he even needed a suppository in the newborn nursey at day of life 3 because of lack of passage of meconium.

What finding would you expect to see during evaluation to explain the patient's symptoms?
A. Presence of rectoanal inhibitory reflex (RAIR) during anorectal manometry.
B. Absence of ganglion cells on rectal biopsy.
C. Absence of transition zone on unprepped contrast enema.
D. Normal sweat chloride study.
E. A and B.

The answers are on page 41

Start screening at age 45?

CRC *from page 1*

findings in Gastroenterology (2022 Jan. doi: 10.1053/j.gastro.2021.12.285), retrospectively reviewed colonoscopy data recorded in the Gastrointestinal Quality Improvement Consortium Registry to address the current knowledge gaps on early-onset CRC. Collected data were for procedures conducted at 123 AMSURG ambulatory endoscopy centers across 29 states between January 2014 and February 2021. In total, 2,921,816 colonoscopies during the study period among patients aged 18-54 years were recorded by AMSURG-associated endoscopists; of these, 562,559 met inclusion criteria for high-quality screening or diagnostic colonoscopy procedures.

The researchers pooled a young-onset age group, including patients between the ages of 18 and 49 years old, in whom 145,998 procedures were performed, including 79,934 procedures in patients aged 45-49 years. A comparator group with 336,627 procedures in patients aged 50-54 years was also included in the study. The findings were categorized into CRC, advanced premalignant lesions (APL), and "any neoplasia," the latter of which included all adenomas, sessile serrated polyps, and CRC.

Among patients aged 18-44 years, the most frequent indications were "diagnostic-other" (45.6%) as well as "diagnostic-bleeding" (39.4%). Among patients between 45 and 49 years of age, the most frequent indications were "screening" (41.4%) and "diagnostic-other" (30.7%). Nearly all (90%) procedures among those aged 50-54 years were for screening.

A multivariable logistic regression identified five variables predictive of either APL or CRC in patients between 18 and 49 years of age: increasing age (odds ratio, 1.08; 95% confidence interval, 1.07-1.08; $P < 0.01$), male sex (OR = 1.67; 95% CI, 1.63-1.70; $P < 0.01$), White race (vs. African American: OR = 0.76; 95% CI, 0.73-0.79, $P < 0.01$; vs. Asian: OR = 0.89; 95% CI, 0.84-0.94, $P < 0.01$), family history of CRC (OR = 1.21; 95% CI, 1.16-1.26; $P < 0.01$) and polyps (OR = 1.33; 95% CI, 1.24-1.43; $P < 0.01$), and examinations for bleeding (OR = 1.15; 95% CI, 1.12-1.18; $P < 0.01$) or screening (OR = 1.20; 95% CI, 1.16-1.24; $P < 0.01$).

The prevalence of neoplastic findings in the young-onset age group increased with increasing age for the categories of any neoplasia, APLs, and CRC. Among patients aged 40-44, 26.59% had any neoplasia, 5.76% had APL, and 0.53% had CRC. In those aged 45-49 years, around 32% had any neoplasia, approximately 7.5% had APLs, and nearly 0.58% had CRC. In the 50- to 54-year-old group, the prevalences of any neoplasia, APL, and CRC were 37.72%, 9.48%, and 0.32%, respectively.

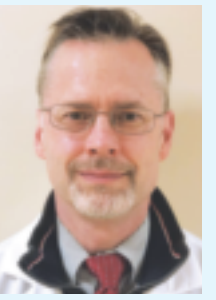
Across all age groups, a family history of CRC was associated with a higher prevalence of any neoplasia and APL. In addition, the rates of any APL and neoplasia in patients with a family history of CRC were comparable to patients who were 5 years older but had no family history of the disease. The researchers noted that their population data are derived from ambulatory endoscopy centers, which may introduce bias associated with insurance coverage or patient preference to attend specific endoscopic centers. Additionally, the investigators stated that many records on race and ethnicity were missing, further limiting the findings.

"The present analysis of neoplastic colorectal pathology among individuals younger than age 50 suggests that lowering the screening age to 45 for men and women of all races and ethnicities will likely detect important pathology rather frequently," they concluded. In addition, the researchers noted that the study results "underscore the importance of early messaging to patients and providers in the years leading up to age 45." Ultimately, improved "awareness of pathology prevalence in individuals younger than age 45 can help guide clinicians in the clinical management of CRC risk," the researchers wrote.

Several of the researchers reported conflicts of interest with Exact Sciences and Freenome. The study received no industry funding. ■

ROMASET/GETTY IMAGES

An alarming trend of increased colorectal cancer (CRC) incidence has been noted among individuals 20-49 years of age over the past 2 decades. This fact combined with the results of microsimulation studies have led all purveyors of CRC screening guidelines in the United States to lower their recommended age for the initiation of average-risk screening from 50 to 45. Despite this major shift in recommendations, relatively little is known about the rates of premalignant neoplasia in this population.



Dr. Ness

The current study by Trivedi et al. presents the results of a massive retrospective cross-sectional study of findings at initial colonoscopy in patients 18-54 who underwent endoscopy at an AMSURG ambulatory surgical center between 2014 and 2021. Data concerning these procedures had previously been collected using the GI Quality Improvement Consortium (GIQuIC) registry. They found that the prevalence of advanced premalignant lesions (APLs) in those 45-49 was almost as high as in those 50-54, and that the prevalence of CRC was even higher. Moreover, 40- to 44-year-olds had APL and CRC prevalence rates almost as high as those aged 45-49. They further found that increasing age, male sex, White race, family history of CRC, and examinations performed for bleeding indications or screening were all associated with higher odds for APLs and CRC. They concluded that these data provide support for lowering the screening age to 45 for all average-risk individuals.

Future studies will need to document the actual effectiveness of CRC screening in persons aged 45-49 and examine the actual cost-benefit of lowering the recommended screening age.

Reid M. Ness, MD, MPH, AGAF, is an associate professor in the division of gastroenterology, hepatology, and nutrition, department of medicine, Vanderbilt University Medical Center, Nashville, Tenn., and at the VA Tennessee Valley Healthcare System, Nashville campus. He is also an investigator in the Vanderbilt-Ingram Cancer Center. Dr. Ness is a study investigator with Guardant Health.

New HBV model may open door to better antivirals

BY WILL PASS
MDedge News

A new mouse model that better represents chronic infection with hepatitis B virus in humans may lead to more effective antiviral therapies for HBV, according to investigators.

During human infection, HBV genomes take the form of covalently closed circular DNA (cccDNA), a structure that has thwarted effective antiviral therapy and, until now, creation of an accurate mouse model, reported lead author Zaichao Xu, PhD, of Wuhan (China) University and colleagues.

"As the viral persistence reservoir plays a central role in HBV infection, HBV cccDNA is the key obstacle for a cure," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology (2021 Dec 9. doi: 10.1016/j.jcmgh.2021.11.011).

Although several previous mouse models have approximated this phenomenon with recombinant cccDNA-like molecules (rcccDNA), the present model is the first to achieve genuine cccDNA, which does not naturally occur in mice.

"Although rcccDNA supports persistent viral replication and antigen expression, the nature of rcccDNA may differ from authentic cccDNA, as additional sequences, like LoxP or attR, were inserted into the HBV genome," the investigators noted.

The new model was created by first constructing an adeno-associated virus vector carrying a replication-deficient HBV1.04-fold genome (AAV-HBV1.04). When injected into mice, the vector led to cccDNA formation via ataxia-telangiectasia and Rad3-related protein (ATR)–mediated DNA damage response, a finding that was confirmed by blocking the same process with ATR inhibitors.

Immediately after injection, mice tested positive for both hepatitis B e antigen and hepatitis B surface antigen, with peak concentrations after either 4 or 8 weeks depending on dose.

Immediately after injection, mice tested positive for both hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg), with peak concentrations after either 4 or 8 weeks depending on dose. HBV DNA was also detected in serum after injection, and 50% of hepatocytes exhibited HBsAg and hepatitis B core protein (HBc) after 1 week. At week 66, HBsAg, HBeAg, and HBc were still detectable in the liver.

"The expression of HBc could only be observed in the liver, but not in other organs or tissues, suggesting that the AAV-HBV1.04 only targeted the mouse liver," the investigators wrote.

Further experimentation involving known cccDNA-binding proteins supported the similarity between cccDNA in the mouse model and natural infection.

"These results suggested that the chromatinization and transcriptional activation of cccDNA formed in this model does not differ from wild-type cccDNA formed through infection."

Next, Dr. Xu and colleagues demonstrated that the infected mice

Continued on following page

Topical steroid shows promise for EoE in early trial

BY JIM KLING
MDedge News

A topical formulation of fluticasone designed to dissolve and coat the esophagus appears safe and effective for the treatment of eosinophilic esophagitis (EoE), according to new results from a phase 2b study. The results pave the way for phase 3 clinical trials.

Topical steroids are frequently used off-label for EoE. They may be repurposed from nebulizers used for asthma, with patients mixing the drugs themselves or sending them to a pharmacy to be compounded. Patients remove the spacer from a nebulizer in order to swallow the active compound or mix the liquid that would be nebulized with honey or Splenda to thicken it to maximize its contact with the esophagus. "Both of these things are very cumbersome and difficult. I get a lot of complaints from patients [that] it doesn't taste good. So, the fact that we have a drug that we are already using, but it's designed for the esophagus, is really exciting," said Nielsen Fernandez-Becker, MD, PhD, of the department of gastroenterology and hepatology at Stanford (Calif.) University. Dr. Fernandez-Becker referred some patients to the trial and performed some procedures.

"I don't think the findings are unexpected, given what we've seen with swallowed inhalers with fluticasone, but I think the real importance of this is that it does look like a dedicated swallow form works. And if this leads to [Food and Drug Administration] approval, then I think that that really becomes a game-changer for this EoE population. Getting something that's FDA approved to treat this disorder is a key unmet need," said John Clarke, MD, AGAF, who was not involved in the study.

He also pointed out that the safety profile of the drug appears good with respect to both candidiasis and adrenal suppression. "It at least seems comparable, if not better than what we're currently doing with the inhaler," said Dr. Clarke, a clinical professor of medicine and director of the esophagus program at Stanford University.

Current options for EoE are limited primarily to the use of proton pump inhibitors and food-elimination diets. Oral budesonide is available to patients in Europe and under investigation in the United States.

"If this leads to [Food and Drug Administration] approval, then I think that that really becomes a game-changer for this EoE population."

The new formulation (APT-1011, Ellodi Pharmaceuticals) is meant to be taken without water and dissolves on the tongue and then coats the esophagus.

In the phase 2b study published in Clinical Gastroenterology and Hepatology (2022 Feb. doi: 10.1016/j.cgh.2022.02.013), researchers randomized 106 adults from six countries with EoE to receive one of four doses of APT-1011, or placebo. Participants had to have current symptoms of dysphagia and active disease after no histologic response from at least 8 weeks of high-dose (20-40 mg/day) proton pump inhibitors. The study included a placebo-controlled, 12-week induction period followed by 40 weeks of maintenance therapy with no placebo arm. The researchers considered a count of fewer than six eosinophils per high-powered field, as measured during an esophageal biopsy, to be a histologic response.

No patients in the placebo group had a response. The response rate was 80% among patients taking a 3-mg dose twice per day; 67% among those taking a 3-mg dose only at bedtime; 86% for those taking 1.5 mg twice per day; and 48% for 1.5 mg only at bedtime ($P < .001$ for all comparisons to placebo).

After 12 weeks, EoE Endoscopic Reference Score (EREFS) improved from 4.5 to 2.3 in the 3-mg b.i.d. group (5.3-2.1 for bedtime only), and from 4.6 to 1.7 for the 1.5-mg b.i.d. group (5.3-2.9 for 1.5 bedtime only). In the placebo group, the change was from 5.2 to 4.5.

Among those who responded during the induction period, the majority continued to be responders at weeks 26 and 52, including the 3-mg b.i.d. group (88% and 69%, respectively), the 3-mg bedtime-only group (79% and 64%), the 1.5-mg b.i.d. group (89% and 84%), and the 1.5-mg bedtime-only group (70% and 30%).

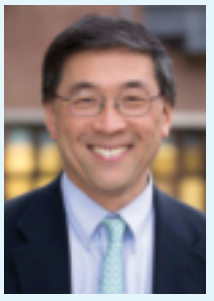
If approved, the new formulation will likely have a big impact on EoE patients, according to Dr. Fernandez-Becker. "The treatment that we decide on ultimately is through shared decision-making with the physician and the patient. I have many patients who want to go with diet, but it's very difficult and it takes a long time to tailor the therapy, and many patients are not interested in proton pump inhibitors. So topical steroids are something that I prescribe a lot for patients," she said.

The fact that the formulation is based on a drug with a known safety record is encouraging, but more research needs to be done. "I don't expect that this would be any different, but that's something that's going to be studied," said Dr. Fernandez-Becker.

The study was funded by Ellodi Pharmaceuticals. Dr. Clarke has no relevant financial disclosures. Dr. Fernandez-Becker has no relevant financial disclosures but was a participant in the study.

Continued from previous page

On the heels of the wondrous development of curative antiviral agents for hepatitis C virus (HCV), renewed attention has been directed to efforts to bring about the cure of HBV. However, this task will hinge on successful elimination of covalently closed circular DNA (cccDNA), a highly stable form of viral DNA that is exceedingly difficult to eliminate. Efforts to develop successful curative strategies will in turn rely on development of small animal models that support HBV cccDNA formation and virus production, which has until recently proved elusive. In the past several years, several mouse HBV models supporting cccDNA formation have been constructed using adeno-associated vector (AAV)–mediated transduction of a linearized HBV genome. Both the AAV-HBV linear episome and cccDNA have been consistently replicated and detected in these models. While they recapitulate the key steps of the viral life cycle, these models do not, however, lend themselves to direct assessment of cccDNA, which have traditionally required detection of cccDNA in the liver.


Dr. Chung

Xu et al. have now developed a novel mouse model in which generation of HBsAg is directly dependent on generation of cccDNA. This dependence thus yields a simple marker for assessment of cccDNA status and allows monitoring of the therapeutic effects of novel agents targeting cccDNA by simply following HBsAg titers. More studies are required to explore the mechanisms underlying HBV cccDNA formation and elimination, but this work suggests a new way forward to tractably evaluate agents that specifically interrupt cccDNA metabolism, an important step in our systematic march toward HBV cure.

Raymond T. Chung, MD, is a professor of medicine at Harvard Medical School and director of the Hepatology and Liver Center at Massachusetts General Hospital, both in Boston. He has no conflicts to disclose.

could serve as a reliable model for antiviral research. One week after injection with the vector, mice were treated with entecavir, polyinosinic-polycytidylic acid (poly[I:C]), or phosphate-buffered saline (PBS; control). As anticipated, entecavir suppressed circulating HBV DNA, but not HBsAg, HBeAg, or HBV cccDNA, whereas treatment with poly(I:C) reduced all HBV markers.

"This novel mouse model will provide a unique platform for studying HBV cccDNA and developing novel antivirals to achieve HBV cure," the investigators concluded.

The study was supported by the National Natural Science Foundation of China, the Fundamental Research Funds for the Central Universities, Hubei Province's Outstanding Medical Academic Leader Program, and others. The investigators reported no conflicts of interest.

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Colorectal ESD succeeds in outpatient setting

BY HEIDI SPLETE
MDedge News

Endoscopic submucosal dissection to remove large colorectal lesions was performed safely and successfully in an outpatient setting, based on data from more than 600 patients.

The widespread adoption of endoscopic submucosal dissection (ESD) has been slow because of its relative complexity, compared with other procedures, wrote Viktor Tidehag, MD, of Danderyd Hospital, Stockholm, and colleagues. The technique, first developed in Japan, is usually an inpatient procedure in Asian countries, the researchers said. However, "We have previously published a study of 156 ESD patients discharged after 2-4 hours of observation post ESD, providing a proof of concept that uncomplicated colorectal ESD can be safely performed as an outpatient procedure," they wrote.

In a study published in Gastrointestinal Endoscopy (2022 Feb. doi: 10.1016/j.gie.2022.02.017), the researchers reviewed data from a larger group of 660 consecutive colorectal ESD procedures at a single center between April 2014 and November 2020. Of these, 48 were planned admission and 612 were scheduled as outpatient procedures. All patients had lesions greater than 20 mm; the median size of the lesions was 38 mm, but the median lesion size was significantly smaller for outpatients, compared with inpatients (37 mm vs. 55 mm). The lesions included 323 (48.9%) in the proximal colon, 102 (15.5%) in the distal colon, and 235 (35.6%) in the rectum. The median procedure duration was 70 minutes, but was significantly shorter for outpatients, compared with inpatients (65 minutes vs. 121 minutes). The mean age of patients in the outpatient and inpatient groups was 68.7 years vs. 70.6 years.

Overall, en bloc resection was achieved in 620 (93.9%) cases, 30 were completed as piecemeal resections, and 10 were aborted and referred for surgical resection. A total of 33 of the scheduled outpatient procedures turned into unplanned inpatient procedures.

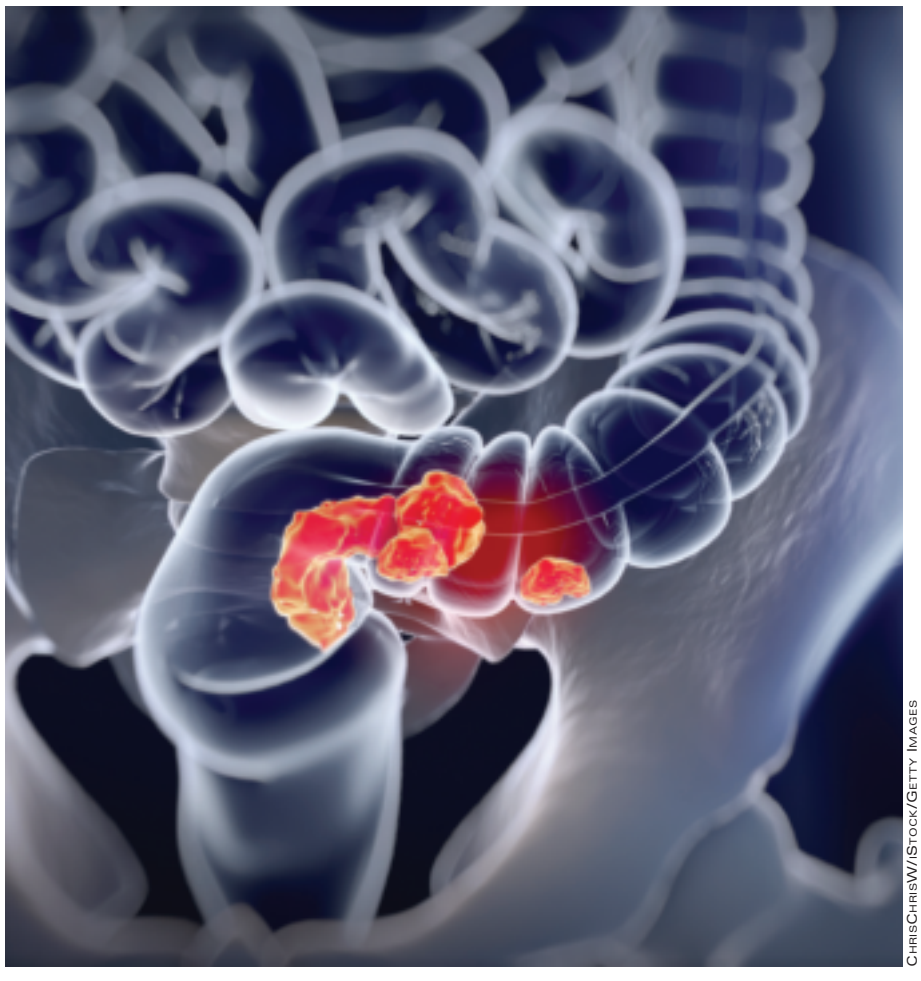
As for intraoperative adverse events, no significant differences in perforation rate occurred between inpatients and outpatients. Overall, perforation occurred in 38 cases (5.8%); 35 of these were treated with clip and 21 also were treated with antibiotics. A total of three patients required emergency surgery following perforations.

Within 30 days of the procedures, 46 patients (7.0%) sought medical attention for possible procedure-related concerns, the researchers said. "No correlation was found between 30-day complications and lesion location, resection speed, age, or perioperative perforation," the researchers wrote in their discussion of the findings.

The procedure "has been slow to gain momentum in the West due to a steep learning curve, long procedural times," and other factors.

The study findings were limited by several factors including the retrospective, nonrandomized design from a single center, with no controls, as well as the potential for selection bias of healthy patients selected for outpatient procedures, and lack of data on comorbidities, the researchers noted. However, the results were strengthened by the inclusion of a large number of lesions in the proximal colon, they said.

Endoscopic treatment is associated with lower mortality and morbidity, as well as lower costs, compared with laparoscopic and open surgery, and ESD could have a significant effect on health economics if widely implemented, the researchers noted in their discussion. "Being able to perform ESD in an outpatient setting compared to an inpatient situation would further decrease treatment costs compared to resection surgery," they said. However, "patients must be well informed about the anticipated postoperative course and potential complications that can arise," particularly in relation to intraprocedural or delayed perforation, they concluded.



ChrisChrisW/iStock/Getty Images

Data support adoption of ESD

The current study was informative and will provide more support for adoption of colorectal ESD in the West, said Salmaan Jawaid, MD, of Baylor College of Medicine, Houston, in an interview.

"Health economics in Asian countries are strikingly different than in other countries and support routine postprocedural admissions for observation," Dr. Jawaid said. "Colorectal ESD has been slow to gain momentum in the West due to a steep learning curve, long procedural times, and the potential for complications with resultant hospital admissions. These logistical elements and impact on health care economics in the West serve as tremendous deterrents [of] adoption of colorectal ESD," he explained.

Dr. Jawaid

"The current study demonstrates colorectal ESD, in a European health care system, may be feasible and safe in an outpatient setting, thereby effectively utilizing health care resources," said Dr. Jawaid. "If admission after colorectal ESD is not routinely needed, health care systems may be more willing to support ESD on a broader scale with a consequent increase in surgery-saving procedures," he noted.

Dr. Jawaid said he was not surprised by the findings overall. "However, I did find it interesting the number of patients who were safely discharged the same day after suffering colonic perforations," he noted. He suspects improved methods of defect closure would explain this, and could in turn increase the rate of adoption.

"In experienced hands, I believe similar results will be attainable in a U.S.-based health care system," he added.

However, "Validated protocol-based clinical pathways are needed in the West before widespread outpatient colorectal ESD is implemented. In the United States, emphasis should be made on the development of long-term educational systems whose primary goal is to ensure proper skills are acquired for endoscopic dissection," he emphasized. "If support from a U.S. health care system is desired on a larger scale, detailed cost-benefit analyses are needed comparing all modalities of colon polyp removal."

The study received no outside funding. The researchers had no financial conflicts to disclose. Dr. Jawaid disclosed serving as a consultant for Lumendi and Conmed.

AGA Clinical Practice Guideline

Systemic therapy for hepatocellular carcinoma

BY JIM KLING
MDedge News

New recommendations from the American Gastroenterological Association focus on choice of systemic therapy in hepatocellular carcinoma (HCC) patients. The guideline authors point out that prognosis and treatment decisions are both heavily dependent on a combination of the severity of underlying disease and biological characteristics of the tumor.

The document includes options for patients who are ineligible for locoregional therapy or resection, patients with metastatic disease and preserved liver function, patients with poor liver function, and patients receiving adjuvant therapy following surgery or locoregional therapy (LRT).

Intermediate or advanced tumor stage is common among HCC patients, and curative options such as surgery and ablation are generally limited to early-stage disease. LRTs – including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and systemic therapy – may be employed against advanced or metastatic HCC, according to the authors, led by Grace L. Su, MD, AGAF, of the division of gastroenterology and hepatology at the University of Michigan, Ann Arbor, and the Veterans Affairs Ann Arbor Healthcare System.

In 2007, the Food and Drug Administration approved the multikinase inhibitor sorafenib as the first systemic therapy for HCC. The new guideline comes in the wake of new systemic therapeutic options that have arrived in the years since, including molecularly targeted therapy and immunotherapy. The authors of the guidance, published in Gastroenterology (2022 Mar;162[3]:920-34), include advice on both first- and second-line therapies.


Dr. Su

Certainty of evidence for the recommendations ranges from low to very low. The recommendations are conditional, and decisions should be made with the values and preferences of the individual patient in mind.

In patients with preserved liver function who are ineligible for LRT or resection, or who have metastatic disease, the authors suggest that first-line treatment should be the combination of atezolizumab and bevacizumab rather than sorafenib. Bevacizumab comes with a bleeding risk, so patients should first be evaluated endoscopically and treated for esophageal varices. For patients who are ineligible for bevacizumab, alternatives are lenvatinib or sorafenib. Patients who are more concerned about disease progression than adverse events may want to consider lenvatinib rather than sorafenib, while those concerned about blood pressure control and who are less concerned about adverse skin reactions may choose sorafenib.

Options for second-line therapy after sorafenib include cabozantinib (mortality reduction, 2.2 months) and pembrolizumab (mortality reduction, 3.3 months). Patients with alpha-fetoprotein levels higher than 400 ng/mL may be candidates for treatment with ramucirumab (mortality reduction, 1.2 months). Another option is regorafenib (mortality reduction, 2.8 months). Patients who are more concerned about adverse effects than a potential survival benefit with any of these therapies may reasonably choose no systemic therapy.

For HCC patients with poor liver function, who are not eligible for LRT or resection, or with metastatic disease, the guidelines recommend against routine use of sorafenib.

In the setting of adjuvant therapy following curative surgical resection, curative local ablation, or TACE LRT, the guidelines recommend against the use of sorafenib. The authors also recommended against the use of bevacizumab following TACE LRT.

The authors noted that there is no high-quality comparative evidence in the second-line setting for atezolizumab plus bevacizumab, sorafenib, or lenvatinib.

The authors disclosed no conflicts. ■

AGA Clinical Practice Update: Commentary

Understanding noninvasive CRC screening options

BY JIM KLING
MDedge News

A new commentary from the American Gastroenterological Association focuses on noninvasive screening options for colorectal cancer (CRC), as well as approaches to ensure quality in noninvasive screening programs. The commentary was published in Gastroenterology (2022 Mar;162[3]:952-6).

The American Cancer Society reported in its Cancer Facts & Figures 2021 report that lifetime risk of CRC in the United States is 4%, and those with above-average risk are recommended to undergo CRC screening at an earlier age, with colonoscopy as a screening modality. Between 75% and 80% of the U.S. population is considered at average risk, and this is the group covered by the expert commentary. In this group, CRC rates jump from 35.1 to 61.2 cases per 100,000 people between the ages of 45-49 years and 50-54 years. Early-onset (before 50) CRC accounts for 12% of all cases and 7% of CRC-related deaths.

The authors noted that the U.S. Preventive Services Task Force made a grade B recommendation for individuals to begin screening at age 45, regardless of screening method (JAMA. 2021 May 18;325[19]:1965-77), and their modeling suggests that screening initialization at 45 rather than 50 years increases life-years gained by 6.2% at the cost of a 17% increase in colonoscopies.

According to the commentary authors, a hybrid approach combining annual fecal immunochemical testing (FIT) at age 45-49, followed by colonoscopy between ages 50 and 70, could result in substantial gains in life-years while prioritizing colonoscopies for advancing age, which is associated with increased risk of advanced adenomas (AA) and CRC.

Exploring options

For stool-based CRC screening, FIT has generally replaced guaiac fecal occult blood testing because of better patient adherence and fewer restrictions on medicine and diet. FIT can produce a quantitative result measured in micrograms of hemoglobin per gram, or qualitatively positive above a threshold of 20 mcg per gram. The MTsDNA (Cologuard) test combines FIT with two DNA methylation markers, KRAS mutation screening, and a measurement of total human DNA, with use of an algorithm of combined results to determine positivity. It is approved only for average-risk individuals aged 45-85.

"The linchpin for effective noninvasive screening programs is adherence, and several measures of adherence are required."

In cases where MTsDNA tests positive, but colonoscopy reveals no findings, an aerodigestive cancer could be present. However, this is considered rare based on a study that revealed that 2.4% of patients with discordant results developed an aerodigestive cancer during a median 5.4 years of follow-up, compared with 1.1% of cases with negative MTsDNA and negative colonoscopy (Clin Gastroenterol Hepatol. 2020 Apr;18[4]:864-71). The difference was not statistically significant. The commentary authors suggest that no further testing is required after a negative high-quality colonoscopy and that patients can resume screening at normal intervals with any of the recommended tests.

The Septin 9 blood test (Epi proColon) is another screening option, and is Food and Drug Administration

Continued on following page

Weekend catch-up sleep may help fatty liver

BY LAIRD HARRISON

People who don't get enough sleep during the week may be able to reduce their risk for nonalcoholic fatty liver disease (NAFLD) by catching up on the weekends, researchers say.

"Our study revealed that people who get enough sleep have a lower risk of developing NAFLD than those who get insufficient sleep," Sangheun Lee, MD, PhD, from Catholic Kwandong University, Incheon, South Korea, and colleagues wrote in Annals of Hepatology (2022 Feb 20. doi: 10.1016/j.aohep.2022.100690).

However, they cautioned that further research is needed to verify their finding.

Previous studies have associated insufficient sleep with obesity, hypertension, diabetes mellitus, and cardiovascular disease, as well as liver fibrosis.

A busy weekday schedule can make it harder to get enough sleep, and some people try to compensate by sleeping longer on weekends. Studies so far have produced mixed findings on this strategy, with some showing that more sleep on the weekend reduces the risk for obesity, hypertension, and metabolic syndrome, and others showing no effect on metabolic dysregulation or energy balance.

Accessing a nation's sleep data

To explore the relationship between sleep patterns and NAFLD, Dr. Lee and colleagues analyzed data from Korea National Health and Nutrition Examination Surveys collected from 2008 to 2019. They excluded people aged less than 20 years, those with hepatitis B or C infections, liver cirrhosis or liver cancer, shift workers and others who "slept irregularly," and those who consumed alcohol excessively, leaving a cohort of 101,138 participants.

The survey didn't distinguish between sleep on weekdays and weekends until 2016, so the researchers divided their findings into two: 68,759 people surveyed from 2008 to 2015 (set 1) and 32,379 surveyed from 2016 to 2019 (set 2).

Set 1 was further divided into those who averaged more than 7 hours of sleep per day and those who slept less than that. Set 2 was divided into three groups: one that averaged less than 7 hours of sleep per day and did not catch up on weekends, one that averaged less than 7 hours of sleep per day and did catch up on weekends, and one that averaged more than 7 hours of sleep throughout the week.

One explanation for the link between sleep patterns and NAFLD is that dysregulation of cortisol, inflammatory cytokines, and norepinephrine are associated with both variations in sleep and NAFLD onset.

The researchers used the hepatic steatosis index (HSI) to determine the presence of a fatty liver, calculated as 8 x (ratio of serum ALT to serum AST) + body mass index (+ 2 for female, + 2 in case of diabetes). An HSI of at least 36 was considered an indicator of fatty liver.

Less sleep, more risk

Participants in set 1 slept for a mean of 6.8 hours, with 58.6% sleeping more than 7 hours a day. Those in set 2 slept a mean of 6.9 hours during weekdays, with 59.9% sleeping more than 7 hours. They also slept a mean of 7.7 hours on weekends.

In set 1, sleeping at least 7 hours was associated with a 16% lower risk for NAFLD (odds ratio, 0.84; 95% confidence interval, 0.79-0.89).

In set 2, sleeping at least 7 hours on weekdays was associated with a 19% reduced risk for NAFLD (OR, 0.81; 95% CI, 0.74-0.89). Sleeping at least 7 hours on the weekend was associated with a 22% reduced risk for NAFLD (OR, 0.78; 95% CI, 0.70-0.87). Compared with those who slept less than 7 hours throughout the week, those who slept less than 7 hours on weekdays and more than 7 hours on weekends had a 20% lower rate of NAFLD (OR, 0.80; 95% CI, 0.70-0.92).

All these associations held true for both men and women.

Why getting your Z's may have hepatic advantages

One explanation for the link between sleep patterns and NAFLD is that dysregulation of cortisol, inflammatory cytokines, and norepinephrine are associated with both variations in sleep and NAFLD onset, Dr. Lee and colleagues wrote.

They also pointed out that a lack of sleep can reduce the secretion of two hormones that promote satiety: leptin and glucagonlike peptide–1. As a result, people who sleep less may eat more and gain weight, which increases the risk for NAFLD.

Ashwani K. Singal, MD, MS, AGAF, a professor of medicine at the University of South Dakota, Vermillion, who was not involved in the study, noted that it was based on comparing a cross section of a population instead of following the participants over time.

"So, I think it's an association rather than a cause and effect," he said in an interview.

Dr. Singal and the study authors all reported no relevant financial relationships. The study was supported by the National Research Foundation of Korea. ■

Continued from previous page

approved for average-risk individuals older than 50 years. It detects methylation of the promoter region of the Septin 9 gene. It has a 48% sensitivity and 91.5% specificity for CRC, as well as a sensitivity of 11.2% for AA. One model found that Septin 9 screening every 1 or 2 years could lead to more quality-adjusted life-years gained and prevention of more deaths than annual FIT, but with more colonoscopies (J Natl Cancer Inst. 2021 Feb 1;113[2]:154-61). CRC screening guidelines do not endorse Septin 9, but screening studies are in progress to assess its performance.

Ensuring quality

"The linchpin for effective noninvasive screening programs is adherence, and several measures of adherence are required," the authors wrote. To ensure high quality of noninvasive screening programs, it is important to create metrics and employ continuous monitoring of compliance, and to initiate changes when adherence and outcomes lag. Important metrics include patient compliance, rapid reporting of test results, timely implementation of follow-up colonoscopies, and systems put in place to restore patients to appropriate CRC screening intervals.

RunPhoto/The Image Bank/Getty Images

The authors suggested several specific metrics and attainable performance goals. The ratio of tests completed within 1 year to tests ordered should reach 90% or more. Outreach should be conducted to patients who do not complete testing within 1 month of the order. All patients should be contacted with 2 weeks of test results, and those who test negative should be made aware of the appropriate interval for future screening, along with the method of contact.

At least 80% of patients who receive a positive test should be offered a colonoscopy date within 3 months, and all within 6 months, because delay past that time is associated with greater risk of AA, CRC, and advanced-stage CRC. Within 6 months of a positive noninvasive test, at least 95% of patients should have undergone a colonoscopy, unless they are too ill, have moved, or cannot be reached. "Quality metrics for noninvasive screening programs should be set and program performance should be measured and ideally reported publicly," the authors summarized. "Poor adherence at any level should trigger review of established protocols and facilitate change to ensure high-quality screening."

Two authors disclosed relationships with Freenome and/or CheckCap, but the third disclosed no conflicts. ■

Model shown to be more accurate

Scoring system *from page 1*

models for assessing AH severity are the Model for End-Stage Liver Disease (MELD); the Age, serum Bilirubin, International normalized ratio, and serum Creatinine (ABIC) score; the Maddrey Discriminant Function (MDF); and the Glasgow Alcoholic Hepatitis Score (GAHS). However, these models have poor accuracy, with the area under the curve is between 0.71 and 0.77.

By comparison, the new model has an accuracy of 86% in predicting 30-day mortality for AH, said coauthor Ashwani K. Singal, MD, MS, professor of medicine at the University of South Dakota Sanford School of Medicine, Sioux Falls.

"This model is certainly timely. We need more accuracy in predicting which patients will recover with medical therapy and which patients won't in the absence of a liver transplant."

"It's a better predictor of the outcome, and that's what sets it apart," he told this news organization. "I think providers and patients will benefit."

He said accuracy in determining the likelihood of death can help clinicians better determine treatment options and prepare patients and their families.

Camille Kezer, MD, a Mayo Clinic resident internist and first author of the paper, said in a statement, "MIAAH also has the advantage of performing well in patients, regardless of whether they've been treated with steroids, which makes it generalizable."

Creating and validating the MIAAH

Researchers analyzed the health records of 266 eligible patients diagnosed with AH between 1998 and 2018 at the Mayo Clinic, Rochester, Minn. The patients collectively had a 30-day mortality rate of 19.2%.

They then studied the effect of several variables, of which the following were found to be significantly associated with mortality: age (P = .002), blood urea nitrogen (P = .003), albumin (P = .01), bilirubin (P = .02), and international normalized ratio (P = .001).

Mayo researchers built the MIAAH model using these variables and found that it was able to achieve a C statistic of 0.86, which translates into its being able to accurately predict mortality more than 86% of the time. When tested in the initial cohort of 266 patients, MIAAH had a significantly superior C statistic compared with several other available models, such as the MELD, MDF, and GAHS, although not for the ABIC.

The researchers then tested the MIAAH model in a validation cohort of 249 patients from health care centers at the University of South Dakota, Sioux Falls, and the University of Kansas, Lawrence. In this cohort, the MIAAH's C statistic decreased to 0.73, which remained significantly more accurate than the MDF but was comparable to that found with the MELD.

Helping with transplant decisions

There are no pharmacologic treatments that can reduce 90-day mortality in severe cases of AH, and only a small survival benefit at 30 days has been reported with prednisolone use.

With a shortage of liver donors, many centers still require 6 months of alcohol abstinence for transplant consideration, although exceptions are sometimes made for cases of early transplant.

A model that more accurately predicts who is at the highest risk of dying within a month can help clinicians decide how best to proceed, Dr. Singal said.

Paul Martin, MD, AGAF, chief of the division of digestive health and liver diseases, Mandel Chair in gastroenterology, and professor of medicine at the University of Miami, told this news organization that the model is potentially important in light of the rising prevalence of AH.

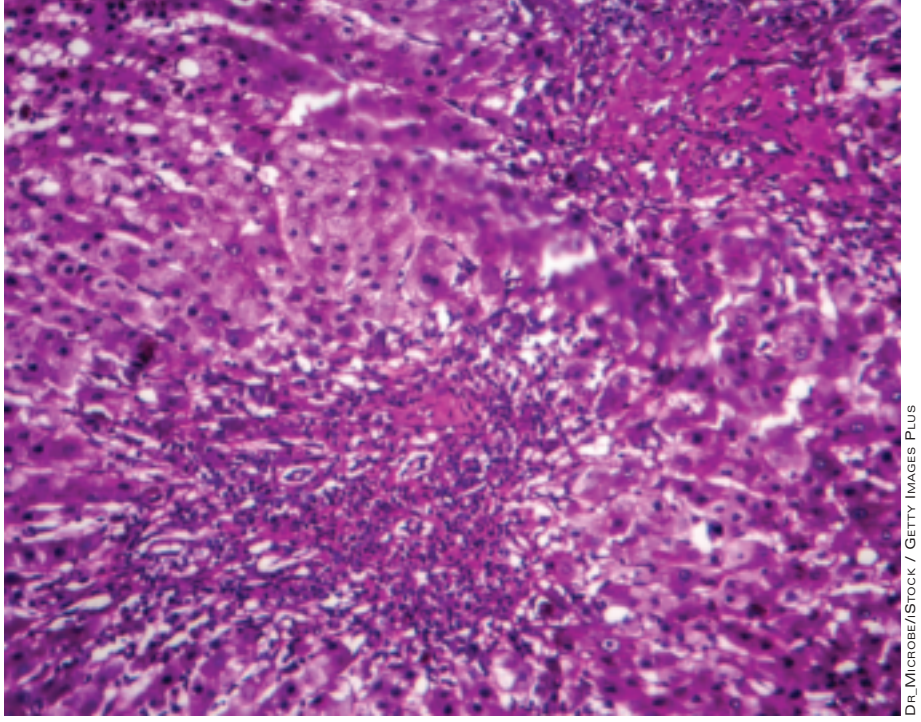
"The numbers of patients with AH are unequivocally increasing and often in young patients," he noted, presenting difficult choices of who to treat with steroids and who to refer for a transplant.

"This model is certainly timely," he said. "We need more accuracy in predicting which patients will recover with medical therapy and which patients won't in the absence of a liver transplant."

He noted, however, that the study's retrospective design requires that it's validated prospectively: "not only looking at the outcome in terms of mortality of patients, but its potential utility in identifying candidates for liver transplantation who are not going to recover on their own."

He said it was unlikely that the model would replace others, particularly MELD, which is ingrained in practices in the United States and other countries, but may instead have a complementary role.

Dr. Singal, Dr. Kezer, and Dr. Martin report no relevant financial relationships. ■



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New index predicts survival in liver disease

BY LAIRD HARRISON

A new prognostic score is more accurate than the commonly used Model for End-Stage Liver Disease (MELD) in predicting post–transjugular intrahepatic portosystemic shunt (TIPS) survival, researchers say.

The Freiburg Index of Post-TIPS Survival (FIPS) could help patients and doctors weigh the benefits and risks of the procedure, said Chongtu Yang, MD, a postgraduate fellow at the Huazhong University of Science and Technology, Wuhan, China.

"For patients defined as high risk, the TIPS procedure may not be the optimal choice, and transplantation may be better," Dr. Yang told this news organization. He cautioned that FIPS needs further validation before being applied in clinical practice.

The study by Dr. Yang and his colleagues was published online Feb. 9 in the American Journal of Roentgenology (2022. doi: 10.2214/AJR.21.27301). To their knowledge, this is the first study to validate FIPS in a cohort of Asian patients.

Decompensated cirrhosis can cause variceal bleeding and refractory ascites and may be life threatening. TIPS can manage these complications but comes with its own risks.

To determine which patients can best benefit from the procedure, researchers have proposed a variety of prognostic scoring systems. Some were developed for other purposes, such as predicting survival following hospitalization, rather than specifically for TIPS. Additionally, few studies have compared these approaches to each other.

A four-way comparison

To fill that gap, Dr. Yang and his colleagues compared four predictive models: the MELD, the sodium MELD (MELD-Na), the Chronic Liver Failure–Consortium Acute Decompensation (CLIF-CAD), and FIPS.

The MELD score uses serum bilirubin, serum creatinine, and the international normalized ratio (INR) of prothrombin time. MELD-Na adds sodium to this algorithm. The CLIF-CAD score is calculated using age, serum creatinine, INR, white blood count, and sodium level. FIPS, which was recently devised to predict results with TIPS, uses age, bilirubin, albumin, and creatinine.

To see which yielded more accurate predictions, Dr. Yang and his colleagues followed 383 patients with cirrhosis (mean age, 55 years; 341 with variceal bleeding and 42 with refractory ascites) who underwent TIPS placement at Wuhan Union Hospital between January 2016 and August 2021.

The most common cause of cirrhosis was hepatitis B infection (58.2% of patients), followed by hepatitis C infection (11.7%) and alcohol use (13.6%).

The researchers followed the patients for a median of 23.4 months. They lost track of 31 patients over that time, and another 72 died. The survival rate after TIPS placement was 92.3% at 6 months, 87.8% at 12 months, and 81.2% at 24 months. Thirty-seven patients received a TIPS revision.

In their first measure of the models' accuracy, the researchers used a concordance index, which compares actual results with predicted results. The number of concordant pairs are divided by the total number of possible evaluation pairs. A score of 1 represents 100% accuracy.

By this measure, the prediction of survival at 6 months was highest for FIPS followed by CLIF-CAD, MELD, and MELD-Na. However, the confidence intervals overlapped.

FIPS also scored highest in the concordance index at 12 and 24 months.

In a second measure of the models' accuracy, the researchers used Brier scores, which calculate the mean squared error between predicted probabilities and actual values. Like the concordance index, Brier scores range from 0.0 to 1.0 but differ in that the lowest Brier score number represents the highest accuracy.

At 6 months, the CLIF-CAD score was the best, at 0.074. MELD and FIPS were equivalent at 0.075, with MELD-Na coming in at 0.077. However, FIPS attained slightly better scores than the other systems at 12 and 24 months.

Six-month survival predictions in patients with cirrhosis

Model	Concordance index	95% confidence interval
FIPS	0.784	0.703-0.865
CLIF-CAD	0.743	0.654-0.832
MELD	0.694	0.603-0.785
MELD-Na	0.699	0.611-0.787

Note: Based on data from 383 patients who underwent TIPS placement.

Source: AJR Am J Roentgenol. 2022 Feb 9. doi: 10.2214/AJR.21.27301.

MDEDGE NEWS

Is FIPS worth implementing?

With scores this close, it may not be worth changing the predictive model clinicians use for choosing TIPS candidates, said Nancy Reau, MD, AGAF, chief of hepatology at Rush University Medical Center, Chicago, who was not involved in the study.

MELD scores are already programmed into many electronic medical record systems in the United States, and clinicians are familiar with using that system to aid in further decisions, such as decisions regarding other kinds of surgery, she told this news organization.

"If you're going to try to advocate for a new system, you really have to show that the performance of the predictive score is monumentally better than the tried and true," she said.

Dr. Yang and Dr. Reau report no relevant financial relationships. ■

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

New Governing Board members

M. Bishr Omary, MD, PhD, AGAF, chair of the AGA Nominating Committee, is pleased to announce that Maria T. Abreu, MD, AGAF, joins the presidential line-up for AGA.

Vice President
Maria T. Abreu, MD, AGAF
Director, Crohn's and Colitis Center
University of Miami

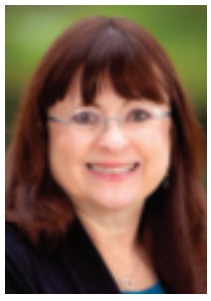

Dr. Abreu

Maria T. Abreu, MD, AGAF, has more than 20 years of leadership experience in basic, translational, and clinical research and mentoring. She is AGA's current councillor at-large, past chair of the AGA Institute Council, and an AGA Institute Council Section Research Mentor Award recipient (2020) for the IMIBD section. Dr. Abreu is also a recipient of the 2019 Sherman Prize by The Bruce and Cynthia Sherman Charitable Foundation that recognizes outstanding achievements in intestinal bowel disease.

The nominating committee also appointed the following slate of councillors which is subject to membership vote.

At-Large Councillor
Kim Barrett, PhD, AGAF
Vice Dean for Research
University of California, Davis

Kim Barrett, PhD, AGAF, is the current chair of the AGA Publications Committee, former chair of the AGA Ethics And Audit Committees, and served twice as director of the Academic Skills Workshop. She was recognized with AGA's top research award, the AGA Distinguished Achievement Award in Basic Science (2021).


Dr. Barrett

Her research interests have centered on the physiology and pathophysiology of the intestinal epithelium and their relevance to inflammatory bowel diseases and diarrheal diseases and have resulted in more than 300 publications.

Councillor for Development and Growth
Lawrence Kosinski, MD, MBA, AGAF
Chief Medical Officer
SonarMD

A serial entrepreneur and thought leader in the world of value-based payment, Larry Kosinski, MD, MBA, AGAF, currently serves as chief medical officer of SonarMD, the leading value-based care coordination solution for complex chronic diseases. He founded SonarMD in 2014 to make it easier for specialists and patients to work together to manage symptomatic chronic illness and prevent clinical deterioration, improving health outcomes and lowering the cost of care.


Dr. Kosinski

In 2021, Dr. Kosinski was selected for his expertise in value-based payment to serve on the Centers for Medicare & Medicaid Services' Physician-Focused Payment Model Technical Advisory Committee and help develop bold, new Medicare payment models.

Education & Training Councillor
Sheryl Pfeil, MD, AGAF
Medical Director and Professor of Clinical Medicine, Clinical Skills Education and Assessment Center
The Ohio State University Wexner Medical Center


Dr. Pfeil

Sheryl Pfeil, MD, AGAF, has been an AGA member for 30 years, serving on the Education and Training Committee, as past chair of the Academy of Educators, as cochair of the AGA future leaders program, and on the editorial board for Gastro Hep Advances. Dr. Pfeil has 30 years of experience in medical education, leading medical student, resident, and fellow education.

Her educational research interests include professional development, training and assessment methods, and virtual education.

Pending approval by the voting membership, all board members begin their terms after DDW 2022. The voting membership will be sent a ballot to approve the slate of councillors on or before March 28, 2022, with a response date of no later than April 29, 2022. Results will be announced at the AGA Annual Business Meeting on June 1, 2022. ■

Five reasons to update your will

You have a will, so you can rest easy, right? Not necessarily. If your will is outdated, it can cause more harm than good. Even though it can provide for some contingencies, an old will can't cover every change that may have occurred since it was first drawn. Professionals advise that you review your will every few years and more often if situations such as the following five have occurred since you last updated your will.

Tetra Images/Getty Images

#1. Family changes
If you've had any changes in your family situation, you will probably need to update your will. Events such as marriage, divorce, death, birth, adoption, or a falling out with a loved one may affect how your estate will be distributed, who should act as guardian for your dependents, and who should be named as executor of your estate.

#2. Relocating to a new state
The laws among the states vary. Moving to a new state or purchasing property in another state can affect your estate plan and how property in that state will be taxed and distributed.

#3. Tax law changes
Federal and state legislatures are continually tinkering with federal estate and state inheritance tax laws. An old will may fail to take advantage of strategies that will minimize estate taxes.

#4. You want to support a favorite cause
If you have developed a connection to a cause, you may want to benefit a particular charity with a gift in your estate. Contact us for sample language you can share with your attorney to include a gift to us in your will.

#5. Changes in your estate's value
When you made your will, your assets may have been relatively modest. Now the value may be larger and your will no longer reflects how you would like your estate divided.

Consider including a gift to the AGA Research Foundation in your will. You will help spark future discoveries in GI. Visit our website at https://gastro.planmylegacy.org or contact us at foundation@gastro.org. ■

2022 AGA Recognition Prize recipients

The American Gastroenterological Association has announced the 2022 recipients of its annual Recognition Prizes, given in honor of outstanding contributions and achievements in gastroenterology.

"AGA is proud to officially announce the exceptional individuals selected for 2022 AGA Recognition Prizes. I wish to thank all the nominators and those who provided nomination letters, and the selection committees for the tough task they had to select among the many superb nominees," said Bishr Omary, MD, PhD, AGAF, chair of the AGA. "Please join us in congratulating this year's distinguished awardees and applauding their contributions to the field of gastroenterology that advance our profession and the patients we serve."

AGA looks forward to celebrating the recipients during Digestive Disease Week® 2022, May 21-24, in San Diego, Calif.

Meet and learn more about our award recipients here: https://gastro.org/membership/recognition-awards/award-winners/.

Take action: Turn up the heat on prior auth

In our recent member survey, 99% of respondents expressed that prior authorization has a negative impact on patients' access to clinically appropriate treatments. We need to continue to put pressure on legislators to eliminate prior authorization burdens.

AGA endorses the Improving Seniors Timely Access to Care Act, which would streamline the prior authorization process in Medicare Advantage by approving in real time commonly approved services and implementing a standardized electronic prior authorization process.

Despite large bipartisan support, we need your help getting this bill across the finish line! Please take 5 minutes to ask your Representative to cosponsor this necessary bill by participating in our campaign.

Go to the AGA action center to contact your lawmakers!

The New Gastroenterologist seeks its next editor-in-chief

AGA's cutting-edge, trainee- and early-career–focused e-newsletter *The New Gastroenterologist* (TNG) is seeking applications for the position of editor in chief (EIC). The role will facilitate the communication of the latest clinical advances among peers and build strong leadership skills managing editorial responsibilities as well as working with reviewers and fellow editors at AGA's journals.

The term is from Oct. 1, 2022 to Sept. 30, 2027, with a transition period starting July 2022.

About TNG

TNG content covers highly relevant clinical topics, such as diverticular hemorrhage and microscopic colitis and diarrhea. Also included in each issue are articles that focus on career pathways, financial and legal matters, perspectives from private practice, brief reviews on clinically relevant topics, issues in clinical medical ethics, and other topics that are relevant to early-career GIs. Each issue also contains an introductory letter from the editor as well as a curated list of relevant articles from the AGA Journals.

Honorarium

The EIC will receive an annual honorarium of $5,000.

Qualifications

- AGA member, between second year of fellowship and 5 years post fellowship.
- Experience identifying and promoting newsworthy content that is relevant to the trainee and early-career GI community, as well as excellent judgment that expands the outstanding reputation of TNG and AGA.
- Experience in medical, scientific, or news-related publishing is preferred, but not required.
- Familiarity with AGA and its priorities, activities, and stances on important issues is ideal, preferably via past volunteer member experience with the association.
- The EIC must be able to devote sufficient time to TNG matters and may not accept editorial appointments to competing publications during their tenure as EIC.

For more information or to apply view the full request for applications.

If you have questions, please contact Ryan Farrell, managing editor, *The New Gastroenterologist*, at rfarrell@gastro.org.

Robust immune response after COVID-19 boosters

BY DAMIAN MCNAMARA

Many people with inflammatory bowel disease (IBD) can mount a strong antibody response to a booster shot of an mRNA COVID-19 vaccine, including those who were unable to respond fully to an initial two-dose vaccine series, new evidence suggests.

Of the study participants, 93% had detectable antibodies after their initial vaccination series, which increased to 99.5% following an additional dose.

"Most IBD patients, including those who are immune suppressed and/or did not have detectable humoral immune responses following the initial mRNA COVID-19 vaccine series, demonstrate strong immune responses to additional doses of mRNA vaccines," Michael D. Kappelman, MD, a pediatric gastroenterologist at the University of North Carolina at Chapel Hill, told this news organization.

"These data support an additional vaccine dose of mRNA vaccine in patients at risk for an inadequate response to the initial series," he said.

Dr. Kappelman presented these findings on behalf of the PREVENT-COVID Study Group as an e-poster at the 17th congress of the European Crohn's and Colitis Organisation.

A study design to measure boosters' benefits

For people with Crohn's disease or ulcerative colitis who are taking immunosuppressants, boosters are generally recommended, Dr. Kappelman and colleagues noted. However, "real-world data on the effectiveness and safety of additional vaccine doses are lacking."

Of the 659 participants, 63% received Pfizer/BioNTech vaccine and 37% received the Moderna vaccine. Five participants received the Johnson & Johnson vaccine.

In 98% of cases, people who received an mRNA vaccine initially also received the same type for the additional dose.

Participants completed baseline and follow-up surveys. Their blood work was obtained and evaluated 8 weeks after completion of the initial vaccine series and 6 weeks after a booster to measure anti–receptor binding domain IgG antibody levels specific to SARS-CoV-2.

Mean increase in antibody levels was 61 mcg/mL in the Pfizer vaccine group and 78 mcg/mL in the Moderna vaccine group following the booster shot.

The main finding that 99.5% of patients had detectable antibodies after an additional dose "is reassuring, as prior studies have suggested some patients did not develop antibodies after the [initial series]."

Of the 47 patients without initial antibody response, 45 (96%) had detectable antibodies following an additional dose.

Serious adverse events (AEs) associated with the booster were rare, Dr. Kappelman said. Among participants, 44% reported no AEs, 24% mild AEs, 25% moderate AEs, and 6% reported serious AEs.

"These data can be used to inform vaccine decisions in patients with a broad array of immune-mediated conditions frequently managed by immunosuppression," the investigators note.

A 'reassuring' finding

"This abstract [gives us] an important understanding about how patients with inflammatory bowel disease respond to COVID-19 vaccination. There have been mixed reports in the prior studies regarding how well patients with IBD respond to vaccination," Jason Ken Hou, MD, said when asked to comment on the research.

The main finding that 99.5% of patients had detectable antibodies after an additional dose "is reassuring, as prior studies have suggested some patients did not develop antibodies after the [initial series]," added Dr. Hou, associate professor of medicine-gastroenterology at Baylor College of Medicine in Houston.

"Further study is still required, as there is more to vaccination response than detectable antibody alone," he added.

Dr. Kappelman and Dr. Hou report no relevant financial relationships. ■

Two factors linked to higher risk of long COVID in IBD

BY DAMIAN MCNAMARA

People with Crohn's disease (CD) who experienced adverse acute COVID-19, defined as requiring hospitalization, were nearly three times more likely to report persistent symptoms 12 weeks after acute infection.

"Long-term, persisting symptoms following COVID-19 is a frequently occurring problem, which is probably underappreciated. IBD [inflammatory bowel disease] specialists should therefore be aware of any of these symptoms and actively ask patients whether they have these problems," lead author Mohamed Attauabi, MD, PhD, said in an interview.

Dr. Attauabi and colleagues were surprised to find that people with ulcerative colitis (UC) who discontinued immunosuppressive agents because of COVID-19 were 1.5 times more likely to experience long COVID symptoms, a result that surprised the researchers.

"This has not been shown before and remains to be confirmed," said Dr. Attauabi, a fellow in the department of gastroenterology at Herlev Hospital, University of Copenhagen.

Dr. Attauabi presented the results as a digital oral presentation at the 17th congress of the European Crohn's and Colitis Organisation.

A closer look at IBD and COVID-19

Large, hospital-based studies of symptoms consistent with long COVID reveal a high prevalence of fatigue, sleep difficulties, and anxiety at 12 weeks or more post acute infection. However, these were not specific to people with IBD, Dr. Attauabi said.

"In patients with IBD, the risk of long-term sequelae of COVID-19 remains to be investigated," he said.

Dr. Attauabi and colleagues studied 197 people with CD and 319 with UC, all of whom had polymerase chain reaction–confirmed COVID-19. Participants were prospectively enrolled in the population-based Danish IBD-COVID registry from Jan. 28, 2020, to April 1, 2021. At a median of 5.1 months, a subset of 85 people with CD and 137 with UC agreed to report any post-COVID symptoms.

In a multivariate analysis, hospitalization for COVID-19 among people with CD was significantly associated with long COVID (odds ratio, 2.76; 95% confidence interval, 1.05-3.90; $P = .04$). Furthermore, people with UC who stopped taking immunosuppressive agents also had a significantly higher risk (OR, 1.50; 95% CI, 1.07-10.22; $P = .01$).

> **"The long-term health effects of COVID-19 did not appear to differ among patients with UC or CD nor according to IBD medications."**

"However, IBD medications such as systemic steroids were not associated with this outcome," Dr. Attauabi said.

Fatigue most common long COVID symptom

Fatigue was the most common long-COVID symptom, reported by 37% of patients with CD and 36% with UC. Anosmia and ageusia were also common, reported by 29% and 28% of patients with CD, and 27% and 19% of those with UC, respectively.

"In our cohort of patients with UC or CD who developed COVID-19, the long-term health effects of COVID-19 did not appear to differ among patients with UC or CD nor according to IBD medications," Dr. Attauabi said.

That is a "great study," said session cochair Torsten Kucharzik, MD, PhD, head of internal medicine and gastroenterology at Lueneburg (Germany) Hospital.

When Dr. Kucharzik asked about smoking, Dr. Attauabi responded that they collected information on current and previous smoking, but they chose not to include the data because they were not statistically significant.

Dr. Attauabi has reported no relevant financial relationships. Dr. Kucharzik has reported receiving grants from Takeda and personal fees from companies including MSD/Essex, AbbVie, Falk Foundation, Biogen, Bristol-Myers Squibb, Arena, Celgene, Celltrion, Ferring, Janssen, Galapagos, Olympus, Mundipharma, Takeda, Amgen, Pfizer, Roche, and Vifor Pharma.

IBD-VTE score serves as reminder to assess postdischarge risk

BY SARA FREEMAN

MDedge News

The chances of developing a blood clot after hospital admission for inflammatory bowel disease (IBD) may persist for several months after being discharged, but a new simple score might help clinicians identify patients who are at greatest risk.

The score – which takes eight, easily captured factors into consideration – had a reasonable ability to distinguish between people who did and did not develop venous thromboembolism (VTE), with an area under the curve of 0.71 (95% confidence interval, 0.69-0.72).

"There is clearly an excess of risk for VTE in patients admitted for IBD in the 90 days following their hospital discharge," said Philip Harvey, MD, a consultant gastroenterologist with the Royal Wolverhampton (England) NHS Trust at the 17th congress of the European Crohn's and Colitis Organisation.

"Advancing age, male gender, emergency admission, longer admissions, and ulcerative colitis are particularly important risk factors," he noted.

"We have proposed a risk-scoring system that will be generalizable to patients under the age of 60 using readily identifiable clinical data so that clinicians can identify patients who are at the greatest risk," Dr. Harvey added at the congress.

"This research provides much needed evidence to guide posthospitalization anticoagulation in patients hospitalized for IBD flares," Bharati Kochar, MD, MS, independently commented.

"Surgeons are already discharging select patients on anticoagulation for DVT [deep vein thrombosis] prophylaxis [but] we need to consider this more systematically after medical IBD admissions," suggested Dr. Kochar, who is a gastroenterologist and IBD specialist at Massachusetts General Hospital in Boston.

"This research should spur prospective investigation into type of anticoagulation upon discharge, dose, duration, and whether the intervention makes a difference in postdischarge clotting events in patients hospitalized for a flare of IBD," she added.

The risk and prevention of thrombosis in IBD was the focus of a recent international consensus project in which IBD and thrombosis experts from 12 countries came together to develop evidence-based guidance (Nat Rev Gastroenterol Hepatol. 2021 Dec;18[12]:857-73).

Large hospitalized IBD population

Dr. Harvey and fellow investigators' IBD-VTE risk score was created using data from almost 102,000 patients (49,385 of whom were men) with just greater than 201,000 hospital admissions between 2006 and 2019. These data were taken from the Hospital Episode Statistics (HES), a "data warehouse" that collects details of all emergency, routine, and outpatient hospital attendances at NHS hospitals in England.

"The HES database is advantageous due to its size because VTE events are relatively uncommon in this group, and therefore it's important to capture as many patients as possible," he explained.

All admissions, from emergencies without surgery to those involving surgery, and those for more routine cases of elective surgery were considered, with the most common (79.3%) admission type being nonsurgical emergencies.

A multilevel logistic regression model was used to identify patient and admission factors that might influence the risk for VTE.

With regard to the number of VTE events seen, Dr. Harvey noted: "There was an enormous excess of events and risk in that 0- to 90-day period, compared to 180-270 days later. This was true across all admission types."

Indeed, VTE rates per 100,000 people in the 0- to 90-day postoperative period were 36.9 for emergency surgical admissions, and 15.6 for both nonsurgical emergencies and elective surgeries. Rates in the later period were a respective 0.84, 1.59, and 1.70.

Dr. Harvey and coinvestigators had no conflicts of interest to disclose. Dr. Kochar is on the Board of Editors for GI & Hepatology News but had no other conflicts of interest.

Removing barriers to high-value IBD care: Challenges and opportunities

BY JOSEPH D. FEUERSTEIN, MD, AGAF; M. ANTHONY SOFIA, MD; SUSHOVAN GUHA, MD, PHD, FASGE, AGAF; AND SARAH STREETT, MD, AGAF


Dr. Feuerstein


Dr. Sofia


Dr. Guha


Dr. Streett

Over the last several years, payer policies that dictate and restrict treatments for patients with inflammatory bowel diseases (IBD) have proliferated. The implementation of new coverage restrictions, expansion of services and procedures requiring prior authorization (PA), and dosing and access restriction to covered drugs, and the requirement of repeated treatment reviews including nonmedical switching for stable patients are widespread. The AGA administered a member needs assessment survey in December 2021 to determine the extent to which these policies harm patients and overburden gastroenterologists and their staff.

Survey findings

Most of the 100 surveyed members reported facing administrative burdens that prevented timely access to patient care. Utilization management practices such as PA, step therapy, and nonmedical switching and dosing restrictions create critical barriers to high-quality GI care for patients with chronic conditions and jeopardize the physician-patient relationship. At a time when physicians have faced unprecedented challenges because of the public health emergency from COVID-19, these burdens also contribute to increasing burnout.

- **Prior authorization:** Among AGA members, 96% of members said that PA is burdensome, with 61% indicating that it is significantly burdensome. Almost 99% of members indicated that PA has a negative impact on patients' access to clinically appropriate treatments; 89% reported that the burden associated with PA has increased over the last 5 years in their practice.
- **Step therapy:** Among members, 87% described the impact step therapy has on their practice as burdensome. Almost 90% of members said step therapy negatively impacted patients' access to clinically appropriate treatments. Almost 90% of members felt that there was an overall negative impact on patient clinical outcomes for those patients who were required to follow a step-therapy protocol.
- **Nonmedical switching and dosing restrictions:** Out of all members, 86% reported an increase in nonmedical switching and dosing restrictions over the last 5 years; 79% of members noted that these restrictions had a negative impact on patient clinical outcomes.

An increasing number of insurance companies are restricting effective biologic therapy to Food and Drug Administration–labeled doses, in direct conflict with current established best practices. It is most concerning that many patients who had been stable on optimized dosing are suddenly notified that they will no longer be able to receive the dose or treatment frequency prescribed by their physician. The concept of optimizing drug therapy based on disease activity and therapeutic drug monitoring is well established, and artificial restrictions to FDA-labeled doses force unnecessary drug deescalation. This transparent effort to reduce costs lacks evidence for safety. Our sickest patients often require higher doses for induction in order to respond, given drug losses, yet some payers refuse to cover the doses these patients require. This new payer-centered effort prioritizes cost containment over the judgment of the treating physician. It causes direct patient harm risking efficacy or loss of response, and subsequent irreversible disease-related complications.

Collaboratively developing aligned incentives can lead us to patient-centered policies that fulfill a shared purpose to optimize the health of people with chronic digestive diseases.

Medicare drug costs

Medicare patients receiving self-injectable or oral medications are not eligible for co-pay assistance programs through pharmaceutical companies because of federal rules. For non-Medicare patients, these programs reduce the co-pay costs to as low as $5 per month. Medicare patients are able to receive infusions like infliximab and vedolizumab at no cost. However, any self-injectable or oral agent can carry a co-pay of over $1,000. Other than for patients meeting income-based eligibility requirements (e.g., below the poverty line), these treatments become prohibitively expensive. Thousands of patients have had to discontinue their self-injectable and/or oral medications because of this cost or have been denied access to the therapy altogether because of cost.

Need for change

These recent changes in insurance policies have resulted in increased harm to our patients with IBD rather than improving the safety or quality of their care. These changes create barriers to disease treatment and have not improved quality of care, patient outcomes, or quality of life. The AGA and other societies have published multiple guidelines and literature on the management of patients with IBD that should serve as the foundation for insurers' medication coverage policies. Additionally, insurance companies should seek input from panels of IBD experts when developing their medication coverage policies to ensure they are patient oriented and facilitate high-quality IBD care.

The following are opportunities for insurers to improve the IBD drug approval process:

- Simplify the appeal process.
- Guarantee rapid response/turnaround to appeal processes to avoid additional delays in care.
- Incorporate experienced expert review by a gastroenterologist.
- Ensure coverage of drug and disease monitoring.
- Integrate expert input in policy development.

Conclusion

Effective patient care in IBD, as well as in other chronic gastrointestinal diseases, requires a collaborative approach to maximize clinical outcomes. It is an exciting time in our field, with rapidly expanding therapeutic options to treat IBD that have the potential to modify the disease course and prevent long-term complications for patients. However, optimizing the use of these treatments to achieve disease remission is challenging and requires the ability to individualize the timely choice of medications at the right dose for each patient to capture and monitor response. The ability to provide individualized, data-driven care is essential to improving the quality of life of our patients, as well as to reducing health care spending over time.

Achieving high-value care is a goal that benefits everyone involved in the health care system. Policies that interfere with timely treatment hurt the very patients that our health care system exists to serve. We cannot stand by while impediments to treatment result in harm to our patients and worsen clinical outcomes. Collaboratively developing aligned incentives can lead us to patient-centered policies that fulfill a shared purpose to optimize the health of people with chronic digestive diseases. ■

Dr. Feuerstein is with the Center for Inflammatory Bowel Disease at Beth Israel Deaconess Medical Center and is an associate professor of medicine at Harvard Medical School, both in Boston. Dr. Sofia is an assistant professor of medicine with the division of gastroenterology and hepatology at Oregon Health and Science University, Portland. Dr. Guha is a professor of medicine at the division of gastroenterology, hepatology, and nutrition and is codirector of the Center for Interventional Gastroenterology at UTHealth (iGUT) at UT Health Science Center, Houston. Dr. Streett is a clinical professor of medicine, gastroenterology, and hepatology and director of the IBD Education and Advanced IBD Fellowship at Stanford (Calif.) Medicine.
The authors reported having no relevant conflicts of interest.

‘Superdonor’ samples don’t increase FMT success

BY SARA FREEMAN
MDedge News

The success of fecal microbiota transplantation (FMT) in people with active ulcerative colitis (UC) was not improved by using highly standardized and controlled “superdonor” samples versus control samples, according to results reported at the 17th congress of the European Crohn’s and Colitis Organisation.

Indeed, a similar percentage (10% and 13.9%, respectively; *P* = .72) of patients achieved combined steroid-free endoscopic and clinical remission at 8 weeks, which was the primary endpoint of the randomized, controlled, RESTORE-UC trial.

“Maybe we were too bold to say we will go for steroid-free endoscopic remission and response,” said Clara Caenepeel, MD, who was the presenting study investigator. “It’s a very strict endpoint.”

The reasoning for such a strict endpoint, however, was so that the trials’ findings could be compared with some of the other studies that have been done with FMT in UC. Importantly, all those trials have all been positive, making the results of the RESTORE-UC trial at odds with their findings.

“I think in the analysis that we will do now is definitely look at how many steps we went into the right direction,” noted Dr. Caenepeel, who is a doctoral researcher at IBD Leuven (Belgium).

Response to results

While some have suggested it was back to the bench to explore negative results, others such as Michael A. Kamm, MBBS, MD, FRCP, FRACP, congratulated the investigators for undertaking the study, saying that “these studies are very hard to do!”

Dr. Kamm, who is professor of gastroenterology and leads the Kamm Gut Research Group at the University of Melbourne, was part of the Australian team that conducted the FOCUS (Faecal Microbiota Transplantation in Ulcerative Colitis) study. That study used the same primary endpoint of steroid-free endoscopic and clinical remission at 8 weeks but reported positive results – 27% of patients who had FMT versus just 8% of those who had a saline enema as a placebo achieved the endpoint (*P* = .021) (Lancet. 2017 Mar 25;389[10075]:1218-28). Similarly positive findings have also been reported from five other studies.

“To understand why [the RESTORE-UC] study is negative, coming after several positive studies, one needs to explore the differences in study design,” Dr. Kamm observed in an interview. Those differences include how donors were selected, how the FMT was delivered, and how patients were selected.

“All the early studies made no presumption about a favorable donor profile,” Dr. Kamm noted. Moreover “the mode of delivery – sigmoidoscopy without any colonoscopic whole-colon delivery, in contrast to previous studies – as well as patient selection, [with] no information on the anatomical extent of their disease,” could be important.

“There are enough robust positive studies of FMT in ulcerative colitis to believe that this therapy can be effective,” said Dr. Kamm. “Analysis of negative studies like this one should help us to understand what factors are needed to achieve a positive outcome.”

Continued on following page

Three popular IBS diets found equivalent

BY LAIRD HARRISON

Three widely followed diets for nonconstipated irritable bowel syndrome (IBS) produce similar results, but traditional dietary advice (TDA) is easier to follow, researchers say.

"We recommend TDA as the first-choice dietary option due to its widespread availability and patient friendliness," Anupam Rej, MBChB, from Teaching Hospitals NHS Foundation Trust in Sheffield, England, and colleagues write.

According to their study, about half the people following each of three diets – TDA; gluten-free; and low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) – reported at least a 50% reduction in their symptoms.

They noted, however, that the low-FODMAP diet produced the most improvement in depression and dysphoria.

The study was published online in Clinical Gastroenterology and Hepatology (2022. doi: 10.1016/j.cgh.2022.02.045).

What the dietary options entailed

The three diets have different origins and methodologies, but all are designed to reduce the abdominal pain, bloating, and altered bowel habits that characterize IBS.

TDA is based on recommendations of the U.K. National Institute for Health and Care Excellence and the British Dietetic Association. It includes "sensible eating patterns," such as regular meals, never having too much or too little, and sufficient hydration. It calls for a reduction in alcoholic, caffeinated, and "fizzy" drinks; spicy, fatty, and processed foods; fresh fruit (a maximum of three per day); and fiber and other gas-producing foods, such as beans, bread, and sweeteners. It also asks people to address any perceived food intolerance, such as dairy.

In North America, the low-FODMAP diet is prescribed as first-line therapy, and the American College of Gastroenterology has given it a conditional recommendation.

FODMAPs are short-chain fermentable carbohydrates found in many fruits, vegetables, dairy products, artificial sweeteners, and wheat. They increase small-intestinal water volume and colonic gas production that can induce gastrointestinal symptoms in people with visceral hypersensitivity.

People following the low-FODMAP diet start by eliminating all FODMAPs for 4-6 weeks, then gradually reintroducing them to determine which are most likely to trigger symptoms.

A gluten-free diet, inspired by what is prescribed to treat celiac disease, has gained popularity in recent years. Although researchers debate the mechanism by which this diet improves symptoms, one leading theory is a reduction in fructans that accompany gluten in foods such as bread.

A rare head-to-head comparison trial

The low-FODMAP diet has proved itself in more clinical trials than the other two approaches, but few, if any, trials have compared them head-to-head in a pragmatic randomized trial, Dr. Rej and colleagues found after reviewing the literature.

They set about filling this gap by recruiting 114 people with IBS and randomly assigning each of them to one of the diets. Ninety-nine people finished the trial, with 33 following each of the diets. People with IBS-constipation were excluded.

Participants were a mean age of 37 years. Seventy-one percent were female, and 88% were White. Their mean IBS symptom severity score was 301, with 9% rating their symptoms as mild, 47% as moderate, and 45% as severe.

The proportion who reported at least a 50% reduction in their symptoms was 58% for the gluten-free diet, 55% for the low-FODMAP diet, and 42% for the TDA. The differences in these proportions were not significant ($P = .43$).

The diets worked about as well regardless of whether the patients had IBS with diarrhea or IBS with mixed diarrhea and constipation.

More on the low-FODMAP diet reported significant improvement in their depression and dysphoria than people on the other two diets.

Changes in anxiety, somatization, and other aspects of IBS quality of life didn't differ significantly with diet.

Where the diets differ: Cost and ease

Fewer people following the TDA rated it as expensive, difficult, or socially awkward, compared with the people following the other two diets.

More of those following the TDA and gluten-free diet found them easy to incorporate into their lives than those following the low-FODMAP diet. About two-thirds of the people in each of these groups said they would consider continuing their diets after the end of the study.

The proportion of people consuming the recommended dietary reference values for macronutrients did not change with any of the diets. However, those in the TDA group reduced their intake of potassium and iron. In the other groups, the researchers noted a reduction in thiamine and magnesium.

Because of COVID-19 restrictions, the researchers were able to collect stool samples from only half of participants. What they did collect showed no difference among the groups in dysbiosis index or functional bacterial profiles.

Baseline factors such as age, gender, IBS subtype, dysbiosis index, somatization, and mood did not predict response to the three diets.

Participants improved as much whether they received dietary instructions face-to-face or through a live virtual consultation.

The study was funded by Schaer. One of the study authors has reported receiving an educational grant from Schaer.

Continued from previous page

RESTORE-UC trial

"Fecal microbiota transplantation is a new emerging strategy in the treatment of active ulcerative colitis," Dr. Caenepeel observed during her presentation. At the time the study was started in 2017 there had been four other studies, with "very heterogeneous" designs in terms of the samples used, the placebos given, the delivery of FMT, and the primary endpoints. The idea of superdonor samples also came out of those trials.

So the aim was to try to standardize practice and set up a trial "to examine if we could increase the FMT success rate in our active ulcerative colitis patients by strictly preselecting our donors; by standardized FMT preparation; and a standardized and repeated FMT administration," Dr. Caenepeel said.

RESTORE-UC was a multicenter, randomized, double-blind, and sham-controlled trial conducted in seven Belgian hospitals. A predefined futility analysis was performed when 66% (n = 72) of the proposed 108 patients had been recruited. Of these, 36 receive autologous FMT and 30 received superdonor FMT.

Dr. Kamm

"We put the emphasis on standardization. This started already with our donor selection," Dr. Caenepeel said. From a potential 57 healthy donors, 15 were selected and altogether provided more than 500 samples that were then whittled down to the ones that provided the "best" microbial content.

FMT or autologous samples delivered four times – first by sigmoidoscopy and then at weekly intervals by rectal enema. Every patient received the same donor material, Dr. Caenepeel stressed, containing the same enterotype and concentration.

In addition to the primary endpoint of steroid-free endoscopic and clinical remission at week 8, secondary endpoints included steroid-free clinical remission, steroid-free clinical response, steroid-free endoscopic remission, and steroid-free endoscopic response. Again, however, no significant differences were seen between the two study arms.

Two serious adverse events were seen in the trial, both in the autologous sample group; these were dysuria/constipation and a worsening of colitis that needed surgery.

In discussion, Walter Reinisch, MD, the director of the inflammatory bowel disease study group at the Medical University of Vienna, picked up on why the study may have been negative. He observed that using a steroid-free endoscopic endpoint, where the Mayo score was zero, may have been a factor. A result of 19% at week 8 was not insignificant, he said.

Perhaps the trials to date have been a little too simplistic by looking at the donor's microbiota, Dr. Caenepeel said. "It goes much further than microbiota." Future work will perhaps look at the genetics and immunity of those undergoing FMT, she suggested.

Dr. Caenepeel, Dr. Kamm, and Dr. Reinisch had no conflicts of interest to disclose.

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AI supports endoscopic evaluation

Assessment *from page 1*

world. If we can get something that will automatically evaluate the disease activity, I think it will be something fantastic," Dr. Peyrin-Biroulet said, "and it's the reason why we were thinking that there is a need for an automated method to measure histological activity in UC."

Old concept enhancing current practice

The idea of using AI systems to aid diagnostics is not new but now makes even more sense in the post–COVID-19 era, suggested Aaron F. Pollett, MD, MSc, FRCPC, codirector of the division of diagnostic medical genetics at Mount Sinai Hospital in Toronto and a pathologist with a specialty interest in gastrointestinal pathology.

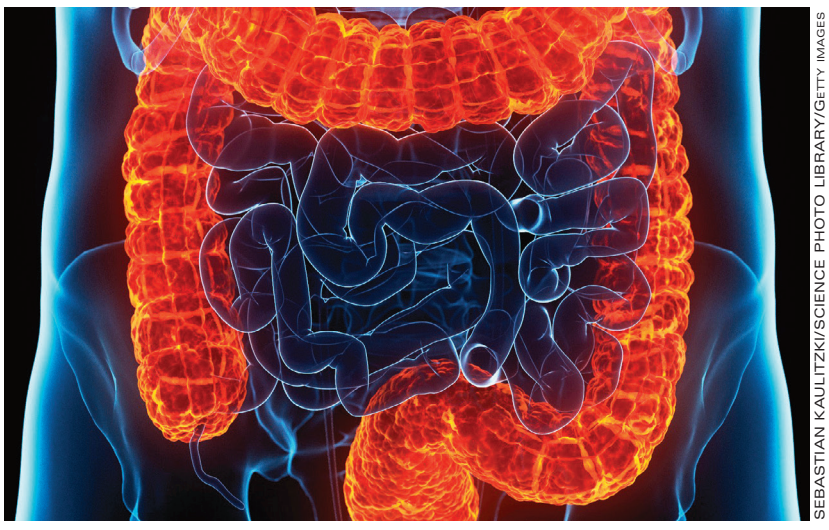
"When we talk about artificial intelligence and histology, there's actually a very long history, it goes back over 30 years," Dr. Pollett said, from assessing cervical samples to its use in breast screening.

What seems to be a sudden flurry of activity in the world of AI and pathology in recent years comes down to having a higher capacity for looking at large images, having access to large data sets, and having a high amount of computing power, Dr. Pollet said. Moreover, "the capacity and the need for whole-slide imaging has really grown especially in the last few years as the pandemic has forced centers to adopt." The need to work remotely and flexibly across centers and the number of available pathologists have also played a role.

AI systems that use image-based retrieval systems are making good headway in IBD, particularly in the diagnosis of UC where "some of the initial research is showing it can be quite good," said Dr. Pollett. The "patchiness that Crohn's can have in comparison to UC" means that it's still an emerging area, but can perhaps be useful for more questionable cases in which "having that degree of certainty can certainly help because there is a discrepancy between specialist and nonspecialist pathologists in the likelihood that what they predict on the biopsy will be the underlying disease."

AI systems in IBD – do they work?

Histopathology is becoming increasingly integrated into IBD clinical trial design at the behest of the Food and Drug Administration and European associations such as ECCO. This can be a tedious procedure that can be prone to error and disagreement between scorers.



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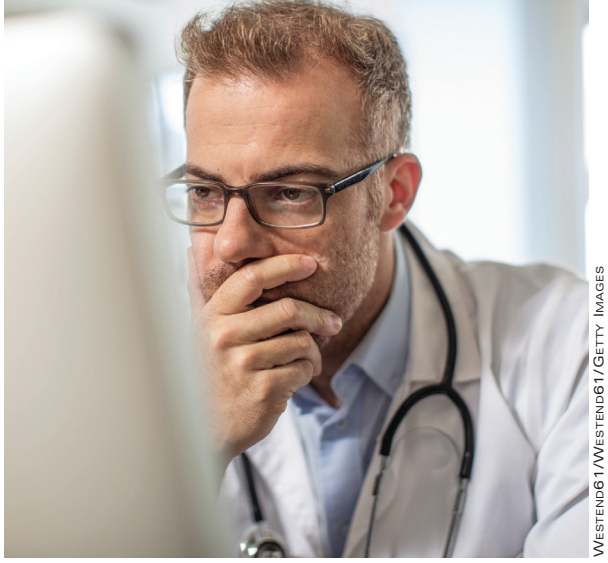
The AI-driven scoring system that Dr. Peyrin-Biroulet and associates have been working on aims to fix all that by using machine learning and image processing to set up a reproducible system. Their system, which is based on the Nancy histological index for UC (Gut. 2017 Jan;66[1]:43-9), shows high correlation (87%) with histopathologists' assessment and was 100% accurate in identifying images with high (grade 4) or no (grade 0) inflammatory activity. The accuracy decreased, however, when trying to distinguish between more moderate activity, with a 75% accuracy for identifying grade 3 and 82% accuracy for grades 1 or 2.



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"I'm actually very fascinated to see how we can be supported by the AI work in our practice," observed Francesca Rosini, a histopathologist working at S. Orsola–Malpighi University Hospital in Bologna, Italy.

Dr. Rosini, who chaired the digital oral presentation session in which Dr. Peyrin-Biroulet had presented, also noted that "obviously for us as well [as AI systems] no activity or severe activity is the easiest part but when it's in between that's where the problems come."

Simplifying histological scoring

Simplifying scoring for use in AI systems could be the key to their future success, as Tommaso Lorenzo Parigi, MD, from Humanitas University in Milan, and a research fellow at the University of Birmingham (England), suggested.

"Histology is particularly important to distinguish between mild activity and remission," Dr. Parigi said. "More than 30 histological scores have been proposed, but their adoption in clinical practice remains limited."

Dr. Parigi has been part of an international team that has developed a simplified histological

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DDSEP 9
Digitive Diseases Self-Education Program

Quick quiz answers

Questions on page 8.

Q1. Correct answer: A. Amyloidosis involving the small intestine

Rationale

This patient has a protein-losing enteropathy as indicated by his diarrhea, peripheral edema, and positive stool alpha-1 antitrypsin test. Multiple diseases, particularly in their later stages, can be associated with a protein-losing enteropathy including primary intestinal lymphangectasia, Crohn's disease of the small intestine, small-intestinal bacterial overgrowth (SIBO), and amyloidosis of the small intestine (A).

Celiac disease (B) is not associated with protein-losing enteropathy. While Crohn's disease can be associated with protein-losing enteropathy, ulcerative colitis (C) is not usually associated with it. Small-bowel dysmotility (D) does not impact absorption or secretion unless associated with SIBO, making this a wrong answer.

Q2. Correct answer: B. Absence of ganglion cells on rectal biopsy.

Rationale

Hirschsprung's disease occurs in approximately 1 out of 5,000 live births and is caused by absence of ganglion cells in the myenteric plexus of the intestine. The condition arises from failure of the neural crest cells to fully migrate caudally along the intestine during early gestation, resulting in a distal portion of the intestine being aganglionic. Rectal and distal sigmoid involvement is seen in around 85% of cases, with the other 15 percent involving more proximal intestine. It can rarely involve the entire colon and small intestine. Ganglion cells inhibit local smooth muscles, resulting in the characteristic inability for aganglionic bowel to relax. This lack of inhibition gives rise to the absence of rectoanal inhibitory reflex (RAIRs) during anorectal manometry. The lack of inhibition also produces a transition zone on contrast enema, with the distal aganglionic bowel being narrow and the more proximal bowel containing ganglia being dilated. Lack of meconium passage in the first 48 hours of life raises concern for Hirschsprung's disease.

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FRONTLINE MEDICAL COMMUNICATIONS

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score based on "the presence of absence of neutrophils, regardless of their number," since these are "key determinants of disease activity."

The score, known as the Paddington International Virtual Chromoendoscopy Score (PICaSSO) Histologic Remission Index (PHRI), has been shown to correlate well with endoscopic outcomes and thus a good measure to include in AI systems. The results of this work were published online in Gut to coincide with the ECCO congress (2022 Feb. doi: 10.1136/gutjnl-2021-326376).

"We are getting close to a world where we could screen biopsies with this kind of systems and consider skipping the pathologists result if AI detected activity," Dr. Parigi provocatively suggested. "Of course, we need to increase and improve our sensitivity, and we are currently working on that to reduce false negatives, as well as training our model to use and apply other histological scores."

Assessing the gut in real time

Perhaps one of the most exciting developments it to be able to use these AI technologies to examine the gut in real time.

"Virtual chromoendoscopy will give you the opportunity to distinguish very carefully all the details of mucosal vascular pattern," said Marietta Iacucci, MD, PhD, FASGE, AGAF, an associate professor and gastroenterology consultant at the Birmingham University Hospitals, England.

"So AI can give you, in real time, the score but at the same time it can help to target, to do biopsies for healing," Dr. Iacucci added when reporting the results of a study evaluating the performance of the first virtual chromoendoscopy AI system to detect endoscopic and histologic remission in UC.

The system was proven to predict endoscopic remission very accurately (94% using PICaSSO and 87% using the UC endoscopic index of severity) when compared with a human endoscopist. Rates of predicting histological remission were also high, at around 83%-85%, depending on the score used.

"For the future, this AI tool can expedite, support, and standardize the endoscopic evaluation of UC mucosal healing in clinical practice and in clinical trials," Dr. Iacucci said.

The next steps are to combine virtual chromoendoscopy with the PHRI and to validate the tool in a multicenter, international PICaSSO-AI study.

The AI-driven scoring system presented by Dr. Peyrin-Biroulet was supported by Takeda. Dr. Peryin-Biroulet acknowledged the receipt of personal fees and grants from Takeda along with multiple other Pharma companies and owning stock options from CTMA. Dr. Iacucci has received research grants from Pentax, AbbVie, Olympus, and Fujifilm and personal fees from Pentax, AbbVie, and Janssen. Dr. Pollett, Dr. Rosini, and Dr. Parigi had no financial conflicts of interest to disclose. ■

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