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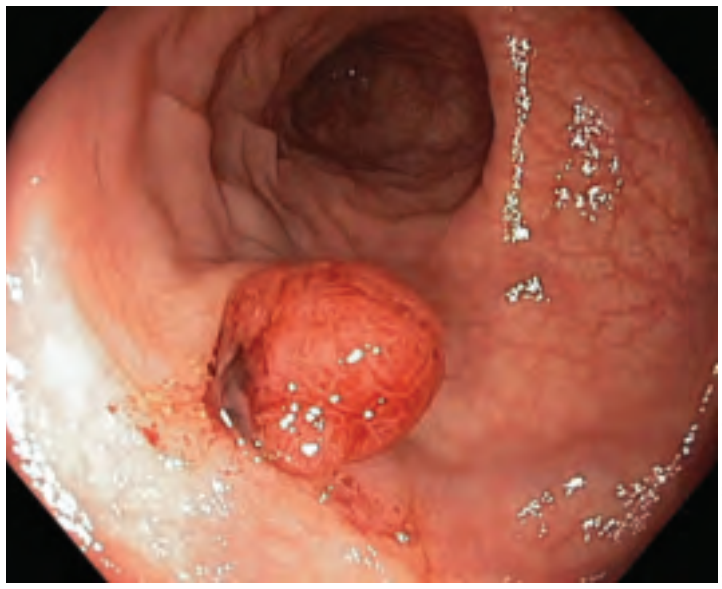

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Colonoscopy in FIT-based screening demands higher ADR

BY MEGAN BROOKS

Adenoma detection rate (ADR) targets for endoscopists performing colonoscopy after a positive fecal immunochemical test (FIT) should be markedly higher compared with ADR targets used in primary colonoscopy, researchers report.

Data from the Netherlands FIT-based screening program show that the ADR is "linearly and inversely" associated with interim colorectal cancer (CRC) occurrence, first author Pieter H.A. Wisse, MD, with Erasmus University Medical Center, Rotterdam, the Netherlands, told this news organization.

"Endoscopists should strive to obtain ADRs as high as possible" in FIT-positive screenees, Dr. Wisse said.

The study was published online in Annals of Internal Medicine (2022 Sep 27. doi: 10.7326/M22-0301).

Small differences, huge consequences

The ADR is a key quality indicator for endoscopists performing colonoscopies for CRC because it reflects

See **Colonoscopy** · *page 18*

Game-changing results seen in acute pancreatitis

Moderate fluid resuscitation advocated

BY MEGAN BROOKS

Early, aggressive fluid resuscitation in acute pancreatitis led to a higher incidence of fluid overload without improving clinical outcomes in the landmark WATERFALL trial.

Early aggressive hydration is widely recommended for the management of acute pancreatitis, but evidence for this practice is limited.

"The WATERFALL trial demonstrates that aggressive fluid resuscitation in acute pancreatitis is not safe, it is not associated with improved outcomes, and it should be abandoned," Enrique de-Madaria, MD, PhD, with Hospital General Universitario Dr. Balmis, Alicante, Spain, told this news organization.

The trial settles a "new and clear reference for fluid resuscitation in this frequent disease: lactated Ringer's solution 1.5 mL/kg per hour (preceded by a 10-mL/kg bolus over 2 hours only in case of hypovolemia)," added Dr. de-Madaria, president of the Spanish Association of Gastroenterology.

"This moderate fluid resuscitation strategy

See **Pancreatitis** · *page 3*

INSIDE

Experts refine nomenclature for eosinophilic GI diseases

BY JIM KLING

MDedge News

A new international consensus paper is recommending that eosinophilic GI diseases (EGIDs) should be named according to more specific criteria. The paper seeks to update nomenclature to improve research and bolster clinical clarity.

The involved part of the GI tract should be specifically named, and the abbreviation "Eo" should be used. Furthermore, the umbrella term should be EGID instead of the currently used "eosinophilic gastroenteritis," according to the statement published

See **Nomenclature** · *page 20*

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THEN AND NOW:
Gut microbiome

BY JONATHAN ROSENBERG, MD, AGAF

In 2007 (coinciding with the inaugural year of GI & Hepatology News), the National Institutes of Health launched the initial phase of the Human Microbiome Project, marking an important milestone in our study and understanding of the gut microbiome. The HMP, which was supported by "only" approximately $20 million of funding in its first year, served as a catalyst for the development of computational tools, clinical protocols, and reference datasets for an emerging field that now approaches nearly $2 billion per year in market value of diagnostics and therapeutics.

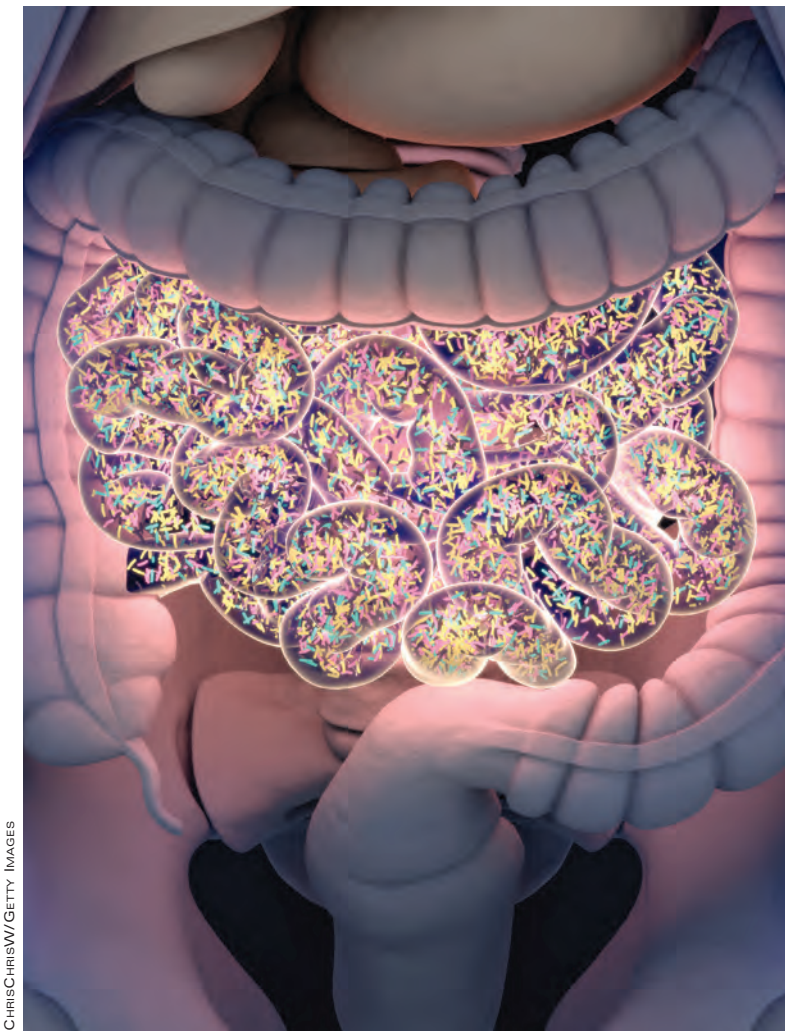
Over the past 15 years, many important discoveries about the microbiome have been made, particularly in the fields of gastroenterology, hepatology, and nutrition. The transplantation of gut microbiome from one person to another has been shown to be more than 90% effective in the treatment of recurrent *C. difficile* infection, disrupting our current therapeutic algorithms of repetitive antibiotics. Other exciting discoveries have included the relationship between the gut microbiome and enteric nervous system, and its roles in the regulation of metabolism and obesity and in the progression of liver fibrosis and cancer.

Several exciting areas related to digestive health and the microbiome are being prioritized for future exploration, including the role of probiotics in nutrition, the complex relationship of the bidirectional "gut-brain" axis, and further development of analytics to define and deliver precision medicine across a wide range of digestive disorders. Without a doubt, emerging microbiome discoveries will be prominently featured in the pages of GI & Hepatology News over the coming years to keep our readers informed of these cutting-edge findings. ■

Dr. Rosenberg

Several exciting areas related to digestive health and the microbiome are being prioritized for future exploration.

Dr. Rosenberg is medical director of the North Shore Endoscopy Center and director of clinical research at GI Alliance of Illinois in Gurnee, as well as an associate editor for GI & Hepatology News. Dr. Rosenberg is a consultant for Aimmune Therapeutics and performs clinical research with Ferring Pharmaceuticals.



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Abandoning early aggressive fluid resuscitation

Pancreatitis *from page 1*

is associated with a much lower frequency of fluid overload and a trend toward improved outcomes. For such reasons, it should be considered as a new standard of care in the early management of acute pancreatitis," Dr. de-Madaria said.

The WATERFALL trial results were published in the New England Journal of Medicine (2022 Sep 15. doi: 10.1056/NEJMoa2202884).

The results are "stunning and, given the carefully crafted trial methods, irrefutable," Timothy Gardner, MD, with the section of gastroenterology and hepatology, Dartmouth–Hitchcock Medical Center, Lebanon, N.H., wrote in a linked editorial (N Engl J Med. 2022 Sep 15. doi: 10.1056/NEJMe2209132).

"Unlike in most other randomized, controlled trials of fluid resuscitation in acute pancreatitis, patients with varying baseline pancreatitis severity were included."

Trial details

The trial was conducted at 18 centers across India, Italy, Mexico, and Spain. Patients who presented with acute pancreatitis were randomly allocated to aggressive or moderate resuscitation with lactated Ringer's solution.

Aggressive fluid resuscitation consisted of a bolus of 20 mL/kg of body weight, followed by 3 mL/kg per hour. Moderate fluid resuscitation consisted of a bolus of 10 mL/kg in patients with hypovolemia or no bolus in patients with normovolemia, followed by 1.5 mL/kg per hour in all patients in this group.

Patients were assessed at 12, 24, 48, and 72 hours, and fluid resuscitation was adjusted according to clinical status.

A total of 249 patients were included in the interim analysis – 122 in the aggressive-resuscitation group and 127 in the moderate-resuscitation group.

The data and safety monitoring board terminated the trial at the first interim safety analysis as a result of the development of fluid overload in 20.5% of the patients in the aggressive-resuscitation group versus 6.3% of those in the moderate-resuscitation group (adjusted relative risk, 2.85; 95% confidence interval, 1.36-5.94; *P* = .004).

"An increased risk of fluid overload was detected in the overall population of patients and also in subgroups of patients without systemic inflammatory response syndrome at baseline, patients with SIRS at baseline (thus, with a higher risk of development of severe pancreatitis), and patients with hypovolemia," the investigators reported.

This clear signal of harm was coupled with no significant difference in the incidence of moderately severe or severe pancreatitis (22.1% in the aggressive-resuscitation group and 17.3% in the moderate-resuscitation group; aRR, 1.30; 95% CI, 0.78-2.18; *P* = .32).

Patients in the aggressive-resuscitation group spent a median of 6 days in the hospital, compared with 5 days for patients in the moderate-resuscitation group.

"These findings do not support current management guidelines, which recommend early aggressive resuscitation for the treatment of acute pancreatitis," the study team wrote.

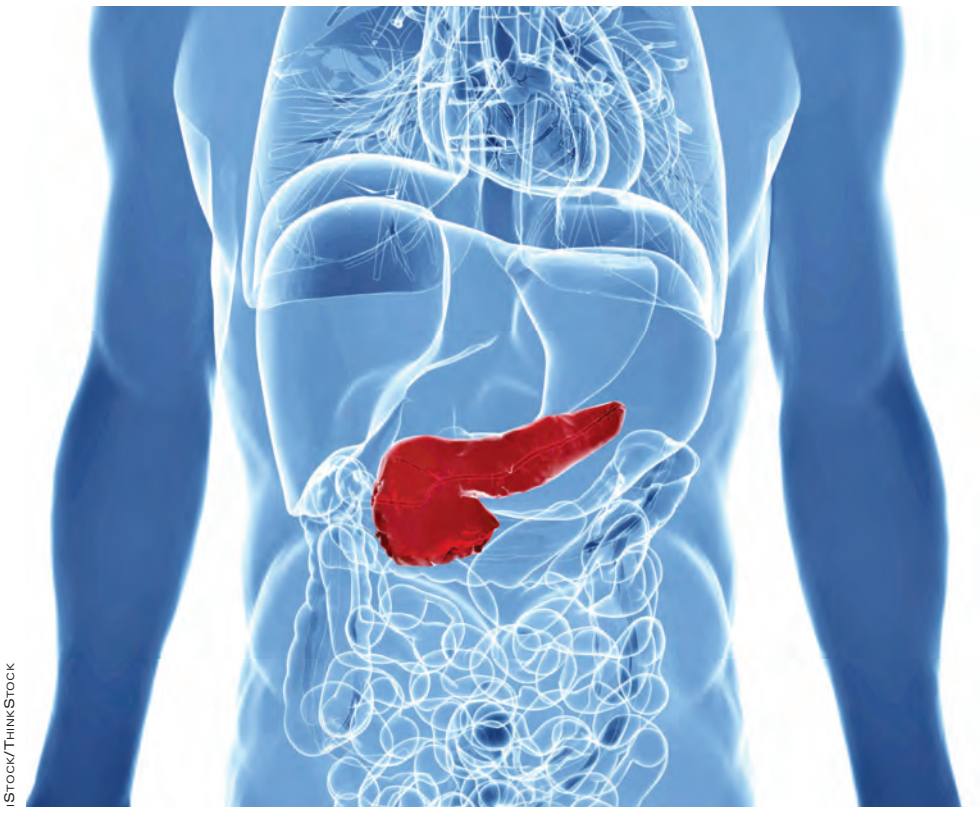
'Landmark' trial

This is a "landmark" trial and "so clinically relevant because of its choice of real world-appropriate aggressive-resuscitation and moderate-resuscitation treatment groups, its use of pancreatitis severity as the main clinical outcome, and its reliance on the carefully defined variable of fluid overload as the main safety outcome," Dr. Gardner wrote in his editorial.

"Unlike in most other randomized, controlled trials of fluid resuscitation in acute pancreatitis, patients with varying baseline pancreatitis severity were included, and changes in the rate of resuscitation were determined on the basis of a dynamic assessment of hemodynamic testing, imaging, and clinical factors," he added.

Dr. Gardner said the WATERFALL trial results lead to several conclusions.

First, the need to focus on a steady rate of initial resuscitation – no more than 1.5 mL/kg of body weight per hour. Clinicians should administer a bolus of 10 mL/kg only if there are signs of initial hypovolemia.



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Second, careful clinical and hemodynamic monitoring are essential during the first 72 hours after admission to make sure that patients remain euvolemic and to avoid fluid overload.

Third, diuresis in patients with fluid overload in the first 72 hours is most likely beneficial and certainly not detrimental to important clinical outcomes.

Dr. Gardner said the trial also highlights the need to focus research efforts on evaluating other pharmacologic therapies instead of crystalloid fluids.

"Performing randomized controlled trials in acute pancreatitis is notoriously difficult, and the limited human and financial resources that are available for appropriately powered trials in this field post WATERFALL are much better spent on comparative-effectiveness and placebo-controlled trials evaluating new therapeutic agents," Dr. Gardner said.

"Now that we have gone over the WATERFALL, it is time to look downstream at new targets to treat this challenging disease," he concluded.

Support for the trial was provided by Instituto de Salud Carlos III, the Spanish Association of Gastroenterology, and ISABIAL (Instituto de Investigación Sanitaria y Biomédica de Alicante).

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz

Q1. A 25-year-old woman with colonic Crohn's disease presents for routine follow-up. She is in remission on her regimen of vedolizumab. When discussing her medication regimen, she asks about the long-term risks associated with her Crohn's disease and treatment.

Which of the following is she at increased risk for because of her diagnosis?

A. Breast adenomas
B. Endometriosis
C. Vaginal atrophy
D. Ovarian cysts
E. Cervical dysplasia

Q2. Which of the following is not a known risk factor for gastric cancer?

A. Lynch syndrome
B. Selenium exposure
C. Menetrier's disease
D. Germline mutation in E-cadherin gene
E. Peutz-Jeghers syndrome

The answers are on page 13.

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Will AI affect the burden of polyp surveillance?

BY MEGAN BROOKS

While the use of artificial intelligence (AI) during colonoscopy may contribute to improved cancer prevention, it may also add to patient burden in terms of increased colonoscopy frequency and, in turn, health care costs, a new study suggests.

The study, published online in Clinical Gastroenterology and Hepatology (2022 Aug 26. doi: 10.1016/j.cgh.2022.08.022), found that colonoscopy plus AI (vs. colonoscopy alone) increased the proportion of patients requiring intensive postpolypectomy colonoscopy surveillance by roughly 35% in the United States and Japan and by about 20% in Europe.

"It's certainly possible that AI will lead to more frequent surveillance for some patients, but it may balance itself out given that recent surveillance guidelines [Gastroenterology. 2020 Mar;158(4):1131-53.e5] have pushed off the surveillance interval depending on the size of the polyp," senior author Seth A. Gross, MD, professor of medicine and clinical chief of the division of gastroenterology and hepatology at New York University Langone Health, said in an interview.

Impact on intensive colonoscopy surveillance

AI tools have been shown to increase the adenoma detection rate (ADR) during colonoscopy, but what impact this has on the frequency of surveillance colonoscopy is unknown.

To investigate, Dr. Gross and an international team conducted a pooled analysis of nine randomized, controlled trials comparing colonoscopy with or without AI detection aids. Five trials were done in China, two in Italy, one in Japan, and one in the United States.

"It's certainly possible that AI will lead to more frequent surveillance for some patients, but it may balance itself out."

The primary outcome was the proportion of patients recommended to undergo intensive surveillance (that is, 3-year interval).

Among a total of 5,796 patients (mean age, 53 years; 51% male), 2,894 underwent AI-assisted colonoscopy and 2,902 underwent standard colonoscopy without AI assistance.

Higher ADRs in the AI-assisted colonoscopy groups were observed in all of the trials.

When the U.S. and Japanese guidelines were followed, the proportion of patients recommended for intensive surveillance increased from 8.4% (95% confidence interval, 7.4%-9.5%) in the non-AI group to 11.3% (95% CI, 10.2%-12.6%) in the AI group, which is an absolute difference of 2.9% (95% CI, 1.4%-4.4%) and a risk ratio of 1.35 (95% CI, 1.16-1.57). When the European guidelines were followed, the increase was from 6.1% (95% CI, 5.3%-7.0%) to 7.4% (95% CI, 6.5%-8.4%), which is an absolute difference of 1.3% (95% CI, 0.01%-2.6%) and a RR of 1.22 (95% CI, 1.01-1.47).

The increases are primarily the result of reallocation of patients from low-risk to intermediate- or high-risk categories, the investigators said. That shift is likely caused by the AI-related increase in adenomas per colonoscopy, which may lead to more effective cancer prevention.

"AI does show us that there's always an opportunity for improvement when we do screening and surveillance colonoscopy," Dr. Gross said. "The goal is the same, which is to offer the highest quality colonoscopy exam and the best possible outcome for our patients, and I think that's what we're starting to see."

Cost analysis needed

Dr. Gross noted that he sees a cost-effectiveness analysis of AI in colonoscopy in the future.

"As this becomes more and more part of regular clinical practice, if it's not being done already, someone will look at the cost-effectiveness of incorporating AI, just like they would for other technologies that come into the area of endoscopy," Dr. Gross said.

Commenting on the study, Atsushi Sakuraba, MD, PhD, a gastroenterologist with University of Chicago Medicine, said he believes that the "benefit of improved adenoma detection and resulting reduction in colon cancer would outweigh the downsides of increased colonoscopy frequency and cost."

"However, an economic impact study would need to be performed to answer this question," added Dr. Sakuraba, who wasn't involved with this study.

The study had no specific funding. Dr. Gross has served as a consultant for Olympus, Cook, Pentax, Ambu, and Iterative Scopes, and served on the advisory board for Docbot. Dr. Sakuraba reported no relevant financial relationships. ■

AGA Clinical Practice Update: Expert Review

Management of refractory celiac disease

BY CAROLYN CRIST
MDedge News

The diagnosis and management of refractory celiac disease remains challenging, but ongoing studies can provide the proper diagnostic criteria and identify the optimal management strategies, according to a new American Gastroenterological Association expert review published in Gastroenterology (2022 Sep 19. doi: 10.1053/j.gastro.2022.07.086).

Celiac disease is present in about 1% of the U.S. population and can cause various symptoms, wrote Peter H.R. Green, MD, director of the Celiac Disease Center at Columbia University, New York, and colleagues. Adhering to a strict gluten-free diet can improve symptoms, normalize serum antibody levels, and reverse small-bowel villous atrophy. However, recurrent or persistent symptoms and elevated celiac antibodies can persist in some patients after a year of adhering to a gluten-free diet, a condition called nonresponsive celiac disease. In some patients, this raises concern for refractory celiac disease, or RCD.

"RCD is believed to occur in only approximately 1% of patients with celiac disease, although this may be an overestimate, as data are obtained from referral centers," the authors wrote.

RCD can be classified into two subtypes with different diagnostic criteria, prognoses, and therapy responses. The first, called RCD1, is characterized by villous atrophy but has intraepithelial lymphocytes similar to conventional celiac disease. The other, called RCD2, is characterized by aberrant clonal T-cell expansion in the intestinal tract and other organs, has a poorer prognosis than RCD1, and has a risk of developing ulcerative jejunitis or enteropathy-associated T-cell lymphoma.

The experts developed 10 clinical practice advice statements based on a review of the published literature and expert opinion.

First, in patients who have persistent or recurring symptoms, an initial celiac disease diagnosis should be confirmed through review of prior diagnostic testing, including serologies, endoscopies, and histologic findings. Celiac disease can overlap with other gastrointestinal conditions, and some pathologic findings aren't specific to celiac disease. Results of serologic testing with tissue transglutaminase immunoglobulin A, deamidated gliadin peptide IgA and IgG, and endomysial antibodies should be reviewed or obtained if not previously performed.

Next, in those with confirmed but nonresponsive celiac disease, ongoing gluten ingestion should be excluded as a cause of symptoms with serologic testing, dietitian review, and potentially detection of immunogenic peptides in stool or urine samples. The authors noted that persistent

Continued on following page

Continued from previous page

gluten ingestion, whether intentional or inadvertent, accounts for 40%-50% of patients with nonresponsive celiac disease. In these cases, esophagogastroduodenoscopy and small-bowel biopsies should be performed to look for persistent villous atrophy, which can also be caused by common variable immunodeficiency, autoimmune enteropathy, tropical sprue, and medication-induced enteropathy. Patients with villous atrophy due to other causes won't respond to a gluten-free diet.

After excluding gluten, clinicians should perform a systematic evaluation for other potential causes of symptoms, including functional bowel disorders, lactose or fructose intolerance, microscopic colitis, pancreatic insufficiency, inflammatory bowel disease, and small-intestinal bacterial growth. Irritable bowel syndrome, for instance, may contribute to persistent symptoms and respond to fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) restriction. RCD should be strongly considered in patients with persistent symptoms or signs of malabsorption after the exclusion of the other causes.

After excluding gluten, clinicians should perform a systematic evaluation for other potential causes of symptoms.

To distinguish between the two subtypes of RCD and exclude enteropathy-associated T-cell lymphoma, clinicians should use flow cytometry, immunohistochemistry, and T-cell receptor rearrangement studies. RCD1 has a normal intraepithelial lymphocyte population, and RCD2 has an aberrant, clonal intraepithelial lymphocyte population. Consulting with a hematopathologist may be necessary to interpret these studies.

After RCD2 is diagnosed, complications such as enteropathy-associated T-cell lymphoma and ulcerative jejunitis should be excluded through small bowel imaging with capsule endoscopy and either computed tomography (CT) or magnetic resonance enterography. In general, the extent and severity of villous atrophy is greater in patients with RCD2, compared with RCD1.

In patients diagnosed with RCD, clinicians should complete a detailed nutritional assessment with investigation of micronutrient and macronutrient deficiencies. Check albumin as an independent prognostic factor. Then, try to correct deficiencies with oral supplements. Malnourished patients may need enteral support, and those with severe malnutrition due to malabsorption may need parenteral support.

So far, RCD management suggestions are based on small retrospective studies and expert opinion, with minimal prospective data and no Food and Drug Administration–approved therapies. The goals should be to improve symptoms and duodenal mucosal abnormalities, manage malnutrition, and prevent lymphoma. Glucocorticoids are considered first-line therapy, typically open-capsule budesonide given as 3 mg three times daily. Prednisone

serves as an alternative with proven efficacy but a higher risk for adverse effects.

The optimal choice for second-line therapy is unknown, but the addition of an immunosuppressant agent to steroids appears to be effective in RCD1, including azathioprine, mercaptopurine, and tioguanine. The best treatment for RCD2 is unknown, though clinical response has been reported with steroids, and cladribine has been well tolerated in some patients.

Patients with RCD who don't respond to steroids may benefit from referral to a center with expertise for management or evaluation for inclusion in clinical trials.

Ultimately, "patients with RCD benefit from evaluation and require regular follow-up by a multidisciplinary team, including gastroenterologist and dietitians, to assess clinical and histologic response to therapy," the authors wrote. "Identify local experts with expertise in celiac disease to assist with management."

The authors reported no grant support or funding sources for this study. One author has received research report from Freenome, and another is on the celiac disease advisory board for Takeda. The remaining authors disclosed no conflicts. ■

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz answers

Questions on page 3.

Q1. Correct answer:
E. Cervical dysplasia.

Rationale

In a nationwide cohort study, women with Crohn's disease and ulcerative colitis were found to have an increased risk of cervical dysplasia. Patients with ulcerative colitis had increased risks of low- and high-grade squamous intraepithelial lesions, whereas patients with Crohn's disease also had increased risks of cervical cancer. Age-appropriate screening with pap smears is important for women diagnosed with inflammatory bowel disease regardless of treatment type.

Reference

Rungoe et al. Clin Gastroenterol Hepatol. 2015 Apr;13(4):693-700.e1.

Q2. Correct answer:
B. Selenium exposure.

Rationale

Helicobacter pylori infection is by far the most important risk factor for gastric cancer worldwide. Less common risk factors for gastric cancer include Lynch syndrome, Peutz-Jeghers syndrome, Menetrier's disease, and germline mutations in the CDH gene (encoding E-cadherin). However, there is some evidence that selenium, as well as high consumption of fruits and vegetables, may have protective effects against gastric cancer.

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Management of antithrombotic medications in elective endoscopy

BY WENFEI WANG, MD, AND NEIL SENGUPTA, MD

Antithrombotic therapy is increasingly used to either reduce the risk of or treat thromboembolic episodes in patients with various medical conditions such as ischemic and valvular heart disease, atrial fibrillation (AF), cerebrovascular disease, peripheral arterial disease, venous thromboembolism (VTE), and hypercoagulable diseases. Antithrombotics include medications classified as anticoagulants or antiplatelets. Anticoagulants work by interfering with the native clotting cascade and consist of four main classes: vitamin K antagonists (VKA), heparin derivatives, direct factor Xa inhibitors, and direct thrombin inhibitors. Direct oral anticoagulants (DOACs) refer to dabigatran (a direct thrombin inhibitor) and the factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban).

Antiplatelets, on the other hand, work by decreasing platelet aggregation and thus preventing thrombus formation; they include P2Y12-receptor inhibitors, protease-activated receptor-1 inhibitors, glycoprotein IIb/IIIa receptor inhibitors, acetylsalicylic acid (ASA), and nonsteroidal anti-inflammatory drugs. All of these agents may directly cause or increase the risk of gastrointestinal bleeding from luminal sources such as ulcers or diverticula, as well as after endoscopic interventions such as polypectomy. However, there is also a risk of thromboembolic consequences if some of these agents are withheld. Thus, the management of patients receiving antithrombotic agents and undergoing GI endoscopy represents an important clinical challenge and something that every GI physician has to deal with routinely.

The goal of this review is to discuss the optimal strategy for managing antithrombotics in patients undergoing elective endoscopy based on current available evidence and published clinical guidelines.[1-4] Much of our discussion will review recommendations from the recently published joint American College of Gastroenterology and Canadian Association of Gastroenterology guidelines on management of anticoagulants and antiplatelets in the periendoscopic period by Abraham et al.[4]

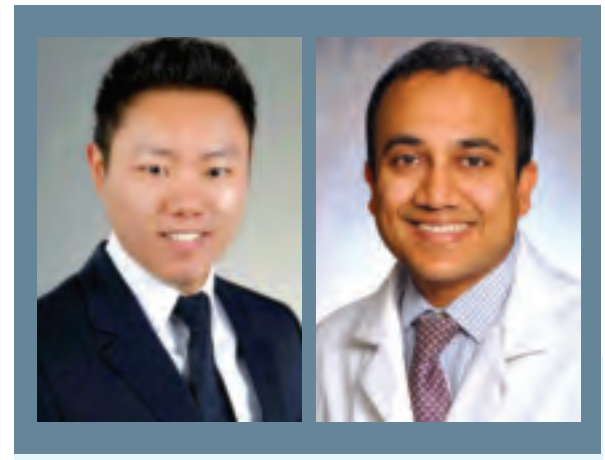
Factors that guide decision-making

The two most vital factors to consider prior to performing endoscopic procedures in patients receiving antithrombotic therapy are to assess the risk of bleeding associated with the procedure and to assess the risk of thromboembolism associated with the underlying medical condition for which the antithrombotic agents are being used. In addition, it is also important to keep in mind the individual characteristics of the antithrombotic agent(s) used when making these decisions.

Estimating procedure-related bleeding risk

Various endoscopic procedures have different risks of associated bleeding. Although guidelines from GI societies may differ when classifying procedures into low or high risk, it is important to know that most of the original data on postprocedural bleeding risks are from studies conducted in patients who are not on complex antithrombotic regimens and thus may not accurately reflect the bleeding risk of patients using newer antithrombotic therapies.[1,4-7]

Traditionally, some of the common low-risk procedures have included diagnostic EGD and colonoscopy with or without biopsy, ERCP without sphincterotomy, biliary stent placement, and push or balloon-assisted enteroscopy. On the other hand, endoscopic procedures associated with interventions are known to have higher bleeding risk, and other procedural factors can influence this risk as well.[8] For example, polypectomy, one of the most common interventions during endoscopy, is associated with bleeding risk ranging from 0.3% to 10% depending on multiple factors including polyp size, location, morphology (nonpolypoid, sessile, pedunculated), resection technique (cold or hot forceps, cold or hot snare), and type of cautery used.[9] For some procedures, such as routine screening colonoscopy, however, the preprocedure estimate of bleeding risk can be uncertain because it is unclear if a high-risk intervention (for example, polypectomy of large polyp) will be necessary. For example, in the most recent ACG/CAG guidelines, colonoscopy with polypectomy less than 1 cm is considered a low/moderate-risk bleeding procedure, whereas polypectomy greater than 1 cm is considered high risk for bleeding.[4] In these situations, the management of antithrombotic medications may depend on the individual patient's risk of thrombosis and the specific antithrombotic agent. In the example of a patient undergoing colonoscopy while on antithrombotic medications, the bleeding risk associated with polypectomy can potentially be reduced by procedural techniques such as preferential use of cold-snare polypectomy. Further high-quality data on the optimal procedural technique to reduce postpolypectomy bleeding in patients on antithrombotic medications is needed to help guide management.



Dr. Wang is a gastroenterology fellow at the University of Chicago. **Dr. Sengupta** is an associate professor at the University of Chicago. They reported no funding or conflicts of interest.

Estimating thromboembolic risk

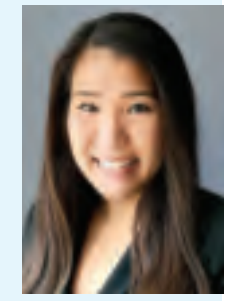
The risk of thromboembolic events in patients who are withholding their antithrombotic therapy for an endoscopic procedure depends on their underlying condition and individual characteristics. In patients who are on antithrombotic therapy for stroke prevention in non-valvular AF, the risk of cerebral thromboembolism in these patients is predictable using the CHA_2DS_2Vasc index.[10] This scoring index includes heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack (TIA), vascular disease, age 65-74 years, and sex categories.

Patients with previous VTE on anticoagulation or those who have mechanical heart valves may have different risk factors for thromboembolic episodes. Among patients with VTE, time from initial VTE, history of recurrent VTE with antithrombotic interruption, and presence of

Antithrombotic medications are increasingly more common, and their periprocedural management for elective endoscopy remains a clinical challenge to gastroenterologists. Important considerations include the risks of the planned procedure and the risks of thromboembolic events while withholding the medication.

The In Focus article for November, which is brought to you by The New Gastroenterologist, reviews the management of antithrombotic medications in elective endoscopic procedure, highlighting the updated guidelines put forth by the Canadian Association of Gastroenterology and the American College of Gastroenterology. The authors, Dr. Wenfei Wang and Dr. Neil Sengupta (University of Chicago), emphasize individualizing the management of antithrombotic medications while providing guideline recommendations on how to navigate the gastrointestinal bleeding risk and cardiovascular disease in this day and age.

Judy Trieu, MD, MPH
Editor in Chief
The New Gastroenterologist



Dr. Trieu

underlying thrombophilia are most predictive of future thromboembolic risk. And for patients with mechanical heart valves, presence of a mitral valve prosthesis, and the presence or absence of associated heart failure and AF determine the annual risk of thromboembolic events. Bioprosthetic valves are generally considered low risk.

In patients with coronary artery disease (CAD), high–thrombosis risk scenarios with holding antiplatelets include patients within 3 months of an acute coronary syndrome (ACS) event, within 6 months of a drug-eluting stent (DES) placement, or within 1 month of a bare-metal coronary stent (BMS) placement. In addition, patients with ACS that occurred within the past 12 months of DES placement or within 2 months of BMS placement are also considered high risk.[11,12] Even beyond these periods, certain patients may still be at high risk of stent occlusion. In particular, patients with a prior history of stent occlusion, ACS- or ST-elevation myocardial infection, prior multivessel percutaneous coronary intervention, diabetes, renal failure, or diffuse CAD are at higher risk of stent occlusion or ACS events with alteration of antithrombotic therapy.[13] Thus, modification of antithrombotic regimens in these patients should be cautiously approached.

Management of antithrombotics prior to elective endoscopy

In patients who need elective endoscopic procedures, if the indication for antithrombotic therapy is short-term, the procedure is probably best delayed until after that period.[13] For patients on long-term or lifelong antithrombotic treatment, the decision to temporarily hold the treatment for endoscopy should occur after a discussion with the patient and all of the involved providers. In some high-risk patients, these agents cannot be interrupted; therefore, clinicians must carefully weigh the risks and benefits of the procedure before proceeding with endoscopy. For patients who are known to be undergoing an elective endoscopic procedure, antithrombotic medications may or may not need to be held prior to the procedure depending on the type of therapy. For example, according to the recent ACG/CAG guidelines, warfarin should be continued, whereas DOACs should be temporarily stopped for patients who are undergoing elective/planned endoscopic GI procedures.

Unfractionated heparin (UFH) administered as a continuous intravenous infusion can generally be held 3-4 hours before the procedure, given its short half-life. Low–molecular weight heparin (LMWH), including enoxaparin and dalteparin, should be stopped 24 hours prior to the procedure.[2,14] Fondaparinux is a synthetic X-a inhibitor that requires discontinuation at least 36 hours preceding a high-risk procedure. For patients on warfarin who are undergoing elective endoscopic procedures that are low risk for inducing bleeding, warfarin can be continued, as opposed to temporarily interrupted, although the dose should be omitted the morning of the procedure.[4] For those who are undergoing high-risk endoscopic procedures (including colonoscopy with possible polypectomy > 1 cm), 5 days of temporary interruption without periprocedural bridging is appropriate in most patients. This is contrary to previous guidelines, which had recommended bridging for patients with a CHA2DS2Vasc score greater than or equal to 2. Recent impactful randomized trials (BRIDGE and PERIOP-2) have called into question the benefit of periprocedural bridging with LMWH. Avoiding bridging anticoagulation was generally found to be similar to bridging in regard to prevention of thromboembolic complications, but importantly was associated with a decreased risk of major bleeding.[15,16] Of note, periprocedural bridging may still be appropriate in a small subset of patients, including those with mechanical valves, AF with CHADS2 score greater than 5, and previous thromboembolism during temporary interruption of VKAs. The decision to bridge or not should ideally be made in a multidisciplinary fashion.[15-20]

In some high-risk patients, these agents cannot be interrupted; therefore, clinicians must carefully weigh the risks and benefits of the procedure before proceeding with endoscopy.

Data are lacking on the ideal strategy for periendoscopic DOAC management. As mentioned above, for patients on DOACs who are undergoing elective endoscopic GI procedures, temporarily interrupting DOACs rather than continuing them is recommended. Currently, there are no randomized controlled trials addressing the management of DOACs in the periendoscopic period. However, based on five cohort studies, the ideal duration of DOAC interruption before endoscopic procedures may be between 1 and 2 days, excluding the day of the procedure.[21-25] This strategy allows for a short preprocedural duration of DOAC interruption and likely provides a balance between bleeding and thromboembolism risk. Importantly, there are no reliable laboratory assays to assess the anticoagulant effect of DOACs, and an individual patient's degree of renal dysfunction may impact how long the DOAC should be held. In general, the anti-Xa drugs should be held for 1-2 days if the creatinine clearance (CrCl) is greater htan or equal to 60 mL/min, for 3 days if the CrCl is between 30 mL/min and 59 mL/min, and for 4 days if the CrCl is less than 30 mL/min.[26] For edoxaban, the recommendation is to hold at least 24 hours before high-risk procedures. The recommendation for stopping dabigatran is 2-3 days before a high-risk procedure in patients with CrCl more than 80 mL/min, 3-4 days prior if between 30 and 49 mL/min, and 4-6 days prior if less than 30 mL/min.[27]

In general, antithrombotic therapy should be resumed upon completion of the procedure unless there remains a persistent risk of major bleeding.

In regard to antiplatelet management, ASA and the $P2Y_{12}$-receptor inhibitors (for example, clopidogrel, prasugrel, and ticagrelor) are the most commonly utilized antiplatelets in patients undergoing endoscopic procedures. For patients who are on ASA monotherapy, whether 81 mg or 325 mg daily, for secondary cardiovascular prevention, no interruption of ASA therapy is necessary for elective procedures. The benefit of ASA for secondary cardiovascular prevention and the possible reduction in thrombotic events seen in randomized controlled clinical trials (RCTs) of nonendoscopic surgical procedures is well known. However, there may be certain exceptions in which aspirin should be temporarily held. For example, short-term interruption of ASA could be considered in high-risk procedures such as biliary or pancreatic sphincterotomy, ampullectomy, and peroral endoscopic myotomy. For patients on single-antiplatelet therapy with a $P2Y_{12}$-receptor inhibitor who are undergoing elective endoscopic GI procedures, the recent CAG/ACG guidelines did not provide a clear recommendation for or against temporary interruption of the $P2Y_{12}$-receptor inhibitor. Although interruption of a $P2Y_{12}$-receptor inhibitor should theoretically decrease a patient's risk of bleeding, the available evidence reported a nonsignificant increased bleeding risk in patients who stop a $P2Y_{12}$ -receptor inhibitor for an elective endoscopic procedure compared with those who continue the medication.[28,29] Therefore, until further data are available, for patients on $P2Y_{12}$-receptor monotherapy, a reasonable strategy would be to temporarily hold therapy prior to high-risk endoscopic procedures, assuming the patients are not at high cardiovascular risk. Clopidogrel and prasugrel have to be stopped 5-7 days prior to allow normal platelet aggregation to resume as opposed to ticagrelor, a reversible $P2Y_{12}$-receptor inhibitor that can be stopped 3-5 days prior.[30]

Lastly, for patients who are on dual-antiplatelet therapy (DAPT) for secondary prevention, continuation of ASA and temporary interruption of the $P2Y_{12}$-receptor inhibitor is recommended while undergoing elective endoscopy. Studies have shown that those who discontinued both had a much higher incidence of stent thrombosis compared with those who remained on aspirin alone.[4,28,31]

Resumption of antithrombotic therapy after endoscopy

In general, antithrombotic therapy should be resumed upon completion of the procedure unless there remains a persistent risk of major bleeding.[1,14] This consensus is based on studies available on warfarin and heparin products, with minimal literature available regarding the resumption of DOACs. The benefits of immediate re-initiation of antithrombotic therapy for the prevention of thromboembolic events should be weighed against the risk of hemorrhage associated with the specific agent, the time to onset of the

Continued on following page

Innovation in GI: What's the next big thing?

How relevant is the AI revolution in GI?

Many thought and industry leaders say that we are in the midst of an AI-revolution in gastroenterology. Indeed, we are at a period of unprecedented growth for deep learning and AI for several reasons, including a recent shift toward data-driven approaches, advancement of machine-learning techniques, and increased computing power. There is, however, also an unprecedented amount of scrutiny and thoughtful conversation about the role AI might play in clinical practice and how we use and regulate these tools in the clinical setting. We are thus in a unique position to ask ourselves the essential question: "Are we on the cusp of an AI revolution in gastroenterology, or are we seeing the release of medical software that is perhaps at best useful in a niche environment and at worse a hype-driven novelty without much clinical benefit?" We will use the most popular use-case, computer-aided detection of polyps in the colon, to explore this question. In the end, I believe that deep-learning technology will fundamentally change the way we practice gastroenterology. However, this is the perfect time to explore what this means now, and what we can do to shape what it will mean for the future.


Dr. Glissen Brown

Jeremy R. Glissen Brown, MD, MSC, is with the division of gastroenterology and hepatology at Duke University Medical Center, Durham, N.C. He has served as a consultant for Medtronic.

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

What's the future of single-use endoscopes?

In 2015, numerous cases of duodenoscope-transmitted infections were reported after endoscopic retrograde cholangiopancreatography procedures. Many, if not most, of these cases were not associated with identified deviations from standard high-level disinfection protocols and occurred at high-volume experienced facilities. A subsequent FDA postmarket surveillance study found contamination rates were linked with potentially pathogenic bacteria in approximately 5% of duodenoscopes. Thus, amid growing concerns about the ability to adequately clean these complex devices, these events prompted the development of single-use duodenoscopes.


Dr. Muthusamy

Given the multifactorial causes leading to contaminated duodenoscopes, the advantages of such single-use devices are their ability to ensure the elimination of the potential of infection transmission as these devices are never reused. In addition to this primary benefit, the ability to create single-use devices could lead to more easily available specialty scopes and allow variations in endoscope design that could improve ergonomics. Single-use devices may also expand the ability to provide endoscopic services by eliminating the need for device reprocessing equipment at low-volume sites. However, several concerns have been raised regarding their use, especially if it were to become widespread. These include issues of device quality and performance (potentially leading to more failed cases or adverse events), cost, their environmental impact, and current uncertainty regarding their indications for use. Furthermore, new alternatives such as reusable devices with partially disposable components or future low-temperature sterilization options may minimize the need for such devices.

V. Raman Muthusamy, MD, MAS, is a professor of clinical medicine at the University of California, Los Angeles, and the medical director of endoscopy at the UCLA Health System. He reported relationships with Medtronic, Boston Scientific, Motus GI, Endogastric Solutions, and Capsovision.

Dear colleagues,
Innovation is the livelihood of our field, driving major advances in endoscopy and attracting many of us to Gastroenterology. From the development of endoscopic retrograde cholangiopancreatography to the wide-spread adoption of third-space endoscopy, we continue to push the boundaries of our practice. But what is the next big disruption in GI, and how will it impact us? In this issue of Perspectives, two experts present their thoughts on current hot topics in GI. Dr. Jeremy R. Glissen Brown discusses the application of artificial intelligence in GI highlighting its promise but also raising important questions. Dr. V. Raman Muthusamy elaborates on single-use endoscopes – are they the wave of the future in preventing infection and meeting patient preference? Or will their long-term cost and environmental impact limit their use? I welcome your own thoughts on disruptive innovation in Gastroenterology – share with us on Twitter @AGA_GIHN and by email at ginews@gastro.org.

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


Dr. Ketwaroo

Continued from previous page

medication, and procedure-specific circumstances. For the small subset of patients on warfarin with a high risk of thromboembolism (for example, mechanical heart valve), bridging with LMWH should be started at the earliest possible time when there is no risk of major bleeding and continued until the international normalized ratio reaches a therapeutic level with warfarin. For patients at a lower risk of thromboembolism, warfarin should be restarted within 24 hours of the procedure. In addition, because of the shorter duration of DOACs, if treatment with these agents cannot resume within 24 hours of a high-risk procedure, bridge therapy should be considered with UFH or LMWH in patients with a high risk of thrombosis.[18] In patients receiving DOACs for stroke prophylaxis in AF, the DOACS can be safely resumed 1 day after low-risk procedures and 2-3 days after high-risk procedures without the need for bridging.[25] All antiplatelet agents should be resumed as soon as hemostasis is achieved.

Conclusion

Antithrombotic therapy is increasingly used given the aging population, widespread burden of cardiovascular comorbidities, and expanding indications for classes of medications such as direct oral anticoagulants. Given the association with antithrombotic medications and gastrointestinal bleeding, it is essential for gastroenterologists to understand the importance, necessity, and timing when holding these medications for endoscopic procedures. Even with the practice guidelines available today to help clinicians navigate certain situations, each patient's antithrombotic management may be different, and communication with the prescribing physicians and including patients in the decision-making process is essential before planned procedures. ■

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

AGA's investment in the future of gastroenterology

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

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

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

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

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

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

AGA President named vice chancellor at UCSD

Everyone at AGA sends our congratulations to AGA President John Carethers, MD, AGAF, on his appointment as the vice chancellor for health sciences at the University of California San Diego.


Dr. Carethers

Dr. Carethers, who began his term as the 117th president of the AGA Institute on June 1, 2022, is returning to UC San Diego after a 13-year tenure at the University of Michigan. He will report directly to the chancellor and serve as a part of the leadership team, effective Jan. 1, 2023.

Aside from his new role at UCSD, Dr. Carethers has been an active member of AGA for more than 20 years and has served on several AGA committees, including the AGA Nominating Committee, AGA Underrepresented Minorities Committee, AGA Research Policy Committee, AGA Institute Council, and the AGA Trainee & Young GI Committee.

We wish him well in this new chapter! ■

Physician views on race, ethnicity, and diversity in GI

The Intersociety Group on Diversity, in partnership with researchers at the University of California, Los Angeles, released results of the first study of its kind to explore perspectives on workforce diversity and health equity among practicing GI and hepatology professionals.

The report – Diversity, Equity, and Inclusion in GI and Hepatology: A Survey of Where We Stand – was published jointly in Gastroenterology, Gastrointestinal Endoscopy, Hepatology, and The American Journal of Gastroenterology. An executive summary is also available in the Journal of Pediatric Gastroenterology and Nutrition.

Key findings:

1. Many are complacent with current levels of diversity. Despite the well-recognized under-representation of certain racial and ethnic groups in GI/hepatology, a small proportion of survey participants (one-third or fewer) felt that racial/ethnic representation was insufficient in the educational/training pipeline, among practicing professionals, or in GI/hepatology leadership. There was a clear discrepancy in satisfaction with workplace diversity among GI and hepatology physicians by race and ethnicity: Overall, 63% of Black physicians were very or somewhat unsatisfied with workplace diversity, whereas 78% of White physicians were very or somewhat satisfied.

2. Interventions are needed. Among those who recommended interventions to enhance racial and gender diversity in the profession, the most common suggestions were to increase the following:

- Mentorship opportunities for resident and medical students who are women or from racial and ethnic populations underrepresented in medicine relative to their numbers in the general population. These groups have traditionally included Latino (that is, Latino/a/x), Black/African American, Native American individuals (namely, American Indians, Alaska Natives, and Native Hawaiians), Pacific Islanders, and mainland Puerto Ricans.
- Representation of underrepresented in medicine GI/hepatology professionals in academic and professional society leadership.

More than 1,200 individuals participated in this nationwide, cross-sectional, 33-question survey. It was developed by University of California, Los Angeles investigators Folasade P. May, MD, PhD, MPhil; Harman Rahal, MD; James H. Tabibian, MD, PhD; and Liu Yang, PhD. The IGD, co-chaired at the time by Darrell M. Gray, II, MD, MPH, and Rachel Issaka, MD, MAS, provided input and facilitated survey distribution. ■

AGA Clinical Practice Update: Expert Review

Management of subepithelial lesions in endoscopy

BY CAROLYN CRIST
MDedge News

The proper management of subepithelial lesions (SELs) depends on the size, histopathology, malignant potential, and presence of symptoms, according to a new American Gastroenterological Association clinical practice update published in Clinical Gastroenterology and Hepatology (2022 Jul 13. doi: 10.1016/j.cgh.2022.05.054).

"SELs are found in 1 in every 300 endoscopies, and two-thirds of these lesions are located in the stomach," explained Kaveh Sharzehi, MD, an associate professor of medicine in the division of gastroenterology and hepatology at Oregon Health & Science University, Portland, and colleagues. "They represent a heterogeneous group of lesions including nonneoplastic lesions such as ectopic pancreatic tissue and neoplastic lesions. The neoplastic SELs can vary from lesions with no malignant potential such as lipomas to those with malignant potential such as gastrointestinal stromal tumors (GISTs). The majority of SELs are small and found incidentally."

The authors developed 10 clinical practice advice statements on the diagnosis and management of subepithelial lesions based on a review of the published literature and expert opinion.

First, standard mucosal biopsies often don't reach deep enough to obtain a pathologic diagnosis for SELs because the lesions have normal overlying mucosa. Forceps bite-on-bite/deep-well biopsies or tunnel biopsies may help to establish a pathologic diagnosis.


Dr. Sharzehi

Used as an adjunct to standard endoscopy, endoscopic ultrasound (EUS) has become the primary method for determining diagnostic and prognostic characteristics of SELs – such as the layer of origin, echogenicity, and presence of blood vessels within the lesion. It can also help with tissue acquisition.

For SELs arising from the submucosa, EUS-guided fine-needle aspiration and fine-needle biopsy have evolved as widely used methods for obtaining tissue. For SELs arising from muscularis propria, fine-needle aspiration and fine-needle biopsy should be used to determine whether the lesion is a GIST or leiomyoma. Using structural assessment and staining will allow for the differentiation of mesenchymal tumors and assessment of their malignant potential.

To remove SELs, multiple endoscopic resection techniques may be appropriate, depending on the layer of origin, size, and location, with the goal of complete, en bloc resection with no disruption to the wall or capsule of the lesion. These techniques should be limited to endoscopists skilled in advanced tissue resection.

SELs without malignant potential, such as lipoma or pancreatic rest, don't need further evaluation or surveillance.

SELs that are ulcerated, bleeding, or causing symptoms should be considered for resection.

Other lesions are managed with resection or surveillance based on pathology. For example, leiomyomas, which are benign and most often found in the esophagus, generally don't require surveillance or resection. On the other hand, all GISTs have some malignant potential, and management varies by size, location, and presence of symptoms. GISTs larger than 2 cm should be considered for resection. Some GISTs between 2 cm and 4 cm without high-risk features can be removed by using advanced endoscopic resection techniques.

The determination for resection in all cases should include a multidisciplinary approach, with confirmation of a low mitotic index and lack of metastatic disease on cross-sectional imaging.

"The ultimate goal of endoscopic resection is to have a complete resection," the authors wrote. "Determining the layer of involvement by EUS is critical in planning resection techniques."

The authors reported no grant support or funding sources for this report. One author serves as a consultant for Boston Scientific, Fujifilm, Intuitive Surgical, Medtronic, and Olympus. The remaining authors disclosed no conflicts. ■

Specific targets for ADR still needed

Colonoscopy *from page 1*

their ability to detect lesions and is inversely associated with the risk of interval postcolonoscopy CRC (PCCRC).

Adults with a positive FIT result have a high prevalence of adenomas, leading to high ADRs for endoscopists performing colonoscopies in this setting. However, data on optimal ADRs of endoscopists performing colonoscopies in FIT-based screening are scarce.

To investigate, Dr. Wisse and colleagues evaluated the association between the ADR and interval PCCRC in patients undergoing colonoscopy after a positive FIT result. The analysis included 362 accredited and audited endoscopists who performed 116,360 colonoscopies.

During a median follow-up of 52 months, 209 interval PCCRCs were identified.

The quality of the colonoscopic examinations in FIT-positive screenees was high; endoscopists' ADRs ranged between 40% and 82%, with a median ADR of 67%.

A higher ADR was strongly associated with lower incidence of interval PCCRC, with an adjusted hazard ratio of 0.95 (95% confidence interval, 0.92-0.97) per 1% increase in ADR.

For endoscopists with an ADR of 60%, the cumulative incidence of interval PCCRC was nearly two times as high as that of endoscopists with an ADR of 70%. The risk was even higher for endoscopists with ADRs less than 60%.

For every 1,000 FIT-positive colonoscopies, the expected number of patients diagnosed with interval PCCRC in 5 years was roughly 2 for endoscopists with an ADR of 70%, compared with almost 3.5 for ADRs of 60% and more than 4.5 for ADRs of 55%.

The authors note that the relatively short duration of follow-up (median, 52 months) could be considered a study limitation.

Quality metrics needed

"These seemingly small ADR differences are deceptive – if an endoscopist increases their ADR by just 10%, their patients' associated decrease in relative interval cancer risk is a remarkable 40% to 50%," Douglas Corley, MD, PhD, MPH, from Kaiser Permanente, Oakland, Calif., points out in an accompanying editorial (2022 Sep 27. doi: 10.7326/M22-2646).

Dr. Wisse and colleagues add that FIT-based colonoscopy has now surpassed primary colonoscopy as the most commonly used primary CRC-screening method.

They say there is a need to determine specific ADR targets for FIT-positive screenees to ensure quality of colonoscopies and optimize the effect of screening programs by reducing interval PCCRC risk.

For primary colonoscopy, most professional societies have recommended an ADR of at least 25% as an indicator of adequate performance. The new study suggests that FIT-positive colonoscopy "demands a markedly higher ADR target than primary colonoscopy," the authors write.

Dr. Corley said this study provides "an excellent framework for evaluating nine concepts regarding effective quality metrics and how these can illustrate pathways for meaningful metrics for the care of other cancers and disorders."

Quality metrics must be trustworthy, important, strategic, relevant, actionable, simple, gaming-resistant, time-stamped, and owned, he explained.

Questions concerning goals, plans for implementation of interventions, and the application of goals while maintaining simplicity must be considered in metric development, Dr. Corley said.

The study had no funding. ■

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THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Finding consensus for EGIDs

Nomenclature *from page 1*

in Clinical Gastroenterology and Hepatology (2022 Feb 15. doi: 10.1016/j.cgh.2022.02.017). The statement included 91 authors from five continents who filled out two rounds of surveys. In total, 93% completed the first and 90% completed the second. The paper produced 22 statements, with a consensus reached on all but 2.

EGIDs are chronic, immune-driven disorders that produce gastrointestinal symptoms and are characterized by eosinophil-dominant inflammation in specific GI regions. Although eosinophilic esophagitis (EoE) is the most well known of these conditions, other EGIDs have become more commonly recognized in recent years and are the subject of intense study. Other affected areas include the stomach, small bowel, and colon, where it can occur individually or in combination.

Efforts are underway to develop guidelines for diagnosis and treatment of EGIDs, but there was initial confusion surrounding the term eosinophilic gastroenteritis since its definition varied significantly in different clinical and research settings, according to the authors. That term varyingly referred to stomach alone, small bowel alone, stomach and small bowel, or any region of the GI tract.

"This nonstandardized use of nomenclature highlighted a need for a common language for non-EoE eosinophilic GI disease names, not only for clinical practice, but also for the consistent data collection required for research to continue to advance the field," co–first authors Evan S. Dellon, MD, MPH, AGAF, from the University of North Carolina at Chapel Hill, and Nirmala Gonsalves, MD, from Northwestern University, Chicago, and colleagues wrote. "This step, while seemingly rudimentary, was essential to inform the guideline efforts that are now underway."

After responses to the surveys were analyzed, respondents participated in one of two scheduled meetings held on a video conferencing platform in May 2021. Feedback from these meetings was then used to create a second round of 29 statements which were again distributed, and participants were asked to either agree or disagree with each statement. Agreement was set a priori at 70%. In all, 38% of the participants were women, and 91% worked in academic or university settings.

In routine clinical practice, conditions with eosinophil-dominant inflammation in the absence of secondary causes outside of the esophagus can collectively be referred to clinically as non-EoE EGID. Stomach involvement should be called eosinophilic gastritis (EoG), small-bowel involvement eosinophilic enteritis (EoN), and colon involvement eosinophilic colitis (EoC).

For research use, and clinical use if desired, the authors called for greater granularity in description of the conditions, with each location named. For example, if the stomach and small bowel are both involved, the condition should be termed eosinophilic gastritis and enteritis. The authors could not reach a consensus for terminology when the esophagus is also involved, leading to the recommendation that it can be included using the phrase "with esophageal involvement" or by using EoE, although they note that this could be confusing since EoE is the current term for eosinophilia isolated in the esophagus.

The authors came to universal agreement in many areas, but there were exceptions that mostly centered on how to name conditions that affect multiple areas of the GI tract. It remains uncertain whether eosinophilia in different regions is caused by the same pathogenesis. Some experts felt that a "primary" location of EGID should be identified using predominant symptoms, endoscopic

features, and complications. However, the authors anticipate that this nomenclature will change over time.

The authors noted that the clinical manifestation of the disease should remain the driving factor behind classification. Testing should be driven by clinically relevant questions and overtesting should be avoided. Future guidelines will likely explore this.

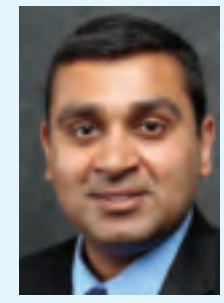
The consensus statement is limited by the fact that most participants were from academic settings. These recommendations do not apply to eosinophilic disorders of gallbladder, liver, or pancreas. Application of the recommendations to the small bowel may be too general or specific, but are meant primarily as a starting point for further refinement.

These limitations should help to drive further research. For example, molecular and pathogenic data could help distinguish EoE from "esophageal involvement" by determining if pathogenic mechanisms are different, which would in turn lead to lumping the conditions into a single term or keeping them separate.

"The iterative and collaborative process led to agreement on nearly all aspects of the proposed nomenclature framework, and has identified future research directions. It is expected that as more data are collected, the nomenclature will again be updated to reflect best practices and the underlying pathogenesis of these disorders," the authors concluded.

The authors disclosed relationships with various industry companies, including AstraZeneca, Celgene, GlaxoSmithKline, Regeneron, Sanofi, and Takeda.

Eosinophilic conditions of the gastrointestinal tract have risen in incidence leading to significant patient symptom and morbidity, but thankfully there have been tremendous innovations in identification, management, treatment, and drug development. In this excellent article, an international consensus was created to reflect the rapidly changing understanding of the phenotypes with updated diagnostic nomenclature.


Dr. Naik

Eosinophilic esophagitis (by far the common eosinophilic GI condition) remains unchanged in its nomenclature, but the prior use of eosinophilic gastroenteritis should no longer be used. Instead, the organ involved – for example, stomach, small bowel, or colon – should be identified, as eosinophilic gastritis, eosinophilic enteritis, or eosinophilic colitis, respectively. This does reflect clinical and patient practice on where biopsies can be routinely obtained from when patients have symptoms. Debates are still ongoing on how to define overlapping sites (for example, simultaneous esophagus and stomach involvement) or if duodenal, jejunal, and ileum eosinophilic conditions should be separated. This new framework will allow us to begin settling these debates based on patient outcomes.

Redefinition of these conditions will help in many aspects. First, advances in therapy targeted as eosinophilic trafficking have been approved with many biologic therapies in the pipeline, and understanding their treatment effects and targets will help our patients. Second, improved nomenclature will help better understand the genetic, phenotypic, and therapeutic options for these conditions providing our patients with personalized care. As the understanding of eosinophilic conditions expands with the growth of genetic associations and drug therapies, we are matching our inflammatory bowel disease colleagues in their successes to provide our patients with personalized care.

Rishi D. Naik, MD, MSCI, is an assistant professor, department of medicine, section of gastroenterology & hepatology, Esophageal Center at Vanderbilt University Medical Center, Nashville, Tenn. He has no conflicts.

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Looking for the source of neuroendocrine tumors

BY JIM KLING
MDedge News

The diversity of neuroendocrine tumors (NETs) – which includes variation in location, mutational profile, and response to therapy – may be due to divergent cellular origins in different tissue sites, according to a new study.

The pathogenesis of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) is poorly understood, in part because of a lack of modeling systems, according to Suzann Duan, PhD, and colleagues. They are a heterogeneous group of tumors that are increasingly prevalent (Clin Gastroenterol Hepatol. 2019 Oct;17[11]:2212-7.e1) in the United States. GEP-NENs arise from endocrine-producing cells and include gastric carcinoids, gastrinomas, and pancreatic NETs.

Despite the general mystery surrounding GEP-NENs, there is at least one clue in the form of the Multiple Endocrine Neoplasia I (MEN1) gene. Both inherited and sporadic mutations of this gene are associated with GEP-NENs. Menin is a tumor-suppressor protein, and previous studies have shown that inactivation of MEN1 leads to loss of that protein and is associated with endocrine tumors in the pancreas, pituitary, and upper GI tract.

In new research published in Cellular and Molecular Gastroenterology and Hepatology (2022 Jul 11. doi: 10.1016/j.jcmgh.2022.06.009), researchers investigated the role of MEN1 in neuroendocrine cell development and traced it to a potential role in the development of NETs.

Patients with MEN1 mutations are at increased risk of gastrinomas, which lead to increased production of the peptide hormone gastrin. Gastrin increases acid production and can lead to hyperplasia in parietal and enterochromaffin cells. These generally develop in Brunner's glands within the submucosa of the duodenum. At time of diagnosis, more than half of such tumors have developed lymph node metastases.

It remains unclear how loss of MEN1 suppresses gastrin production. Previous research showed that homozygous MEN1 deletion in mice is lethal to embryos, while leaving one copy intact leads to heightened risk of endocrine tumors in the pancreas and pituitary gland, but not in the GI tract. The studies did not reveal the tumor's origin cell.

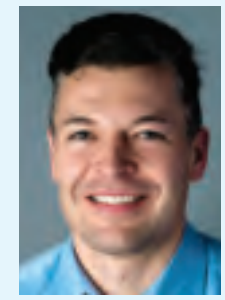
The researchers developed a novel mouse model in which MEN1 is conditionally deleted from the GI tract epithelium. This led to hyperplasia of gastrin-producing cells (G cells) in the antrum, as well as hypergastrinemia and development of gastric NETs. Exposure to a proton pump–inhibitor accelerated gastric NET development, and the researchers identified expansion of enteric glial cells that expressed gastrin and glial fibrillary acidic protein (GFAP). Glial cells that differentiated into endocrine phenotype were associated with a reversible loss of menin. "Taken together, these observations suggest that hyperplastic G cells might emerge from reprogrammed neural crest–derived cells in addition to endoderm-derived enteroendocrine cells," the authors wrote.

That idea is supported by previous research (Science. 2017 Jul 7. doi: 10.1126/science.aal3753) indicating that multipotent glial cells expressing GFAP or SOX10 may play a developmental role in formation of neuroendocrine cells.

With this in mind, the researchers deleted MEN1 in GFAP-expressing cells to see if it would promote neuroendocrine cell development.

The result was hyperplasia in the gastric antrum and NETs in the pituitary and pancreas. To the researchers' surprise, NET development was associated with

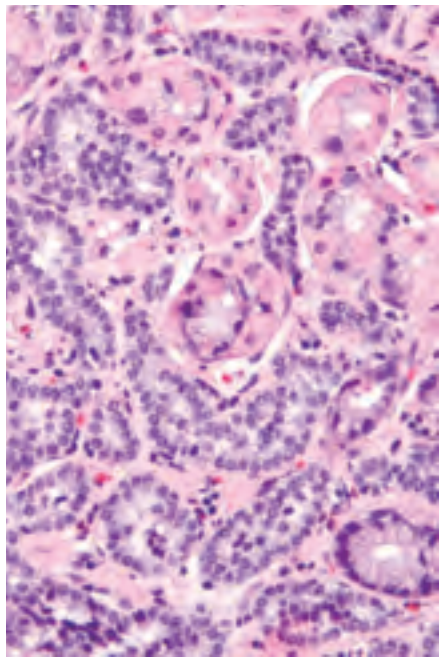
Gastroenteropancreatic neuroendocrine neoplasms share endocrine and neural features but are diverse in terms of their location, behaviors, and response to therapies. One explanation for heterogeneity in GEP-NENs is that they have diverse cellular origins. The study by Duan and colleagues suggests that glia could be a potential cell of origin in GEP-NENs. GEP-NEN development in the pancreas, pituitary, and upper gastrointestinal tract is associated with mutations in the Multiple Endocrine Neoplasia I (MEN1) gene that cause a loss of the tumor-suppressor protein menin.


Dr. Gulbransen

The authors found that deleting MEN1 only in glial fibrillary acidic protein (GFAP)–expressing cells leads to the development of pancreatic and pituitary neuroendocrine tumors and changes to the epithelial lining of the stomach. These observations suggest a role for menin in glial development and/or maturation that, when lost, can contribute to cellular reprogramming toward a neuroendocrine fate. However, it is also possible that deleting MEN1 affects the developmental trajectories of GFAP-expressing progenitor cells rather than reprogramming mature glia. Interestingly, tumor development and neuroendocrine reprogramming were observed only in the pituitary, pancreas, and stomach, and did not seem to occur in other organs with large populations of similar GFAP-positive cells such as the brain, spinal cord, or other peripheral organs. This seems to indicate specialized developmental roles of menin in these locations or that glia in the pituitary, pancreas, and stomach exhibit a heightened plastic potential that differs from other populations of glia.

The tumorigenic potential of GFAP-positive cells differs even between the pituitary, pancreas, and stomach since mice lacking MEN1 in GFAP-positive cells did not develop gastrinomas while tumors were observed in the pituitary and pancreas. This could indicate that additional drivers are necessary to promote NENs in the intestine which are not required in other locations. These differences could be important when considering treatment strategies given the diverse nature of the cells and mechanisms involved.

Brian D. Gulbransen, PhD, is an associate professor in the department of physiology and an MSU Foundation Professor at Michigan State University, East Lansing. He has no conflicts.



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Histologic view shows neuroendocrine tumor under microscope.

loss of GFAP expression as well as activation of neuronal and neuroendocrine-related genes in the stomach, pancreas, and pituitary. There was universal reduction of GFAP protein expression in pituitary and pancreatic NETs, but GFAP transcript levels stayed steady in the gastric antra despite a reduction in GFAP-reporter expression. This could indicate that the menin protein interacts with GFAP. If so, eliminating menin in GFAP-positive cells could change the localization of GFAP, which may in turn lead to changes in glial cell identity.

When the researchers compared transcriptomes of hyperplastic antral tissues to well-differentiated NETs, they found that NETs exhibited a greater loss of glial-restricted progenitor lineage–associated genes as well as more downregulation of gliogenesis-directing factors. "Thus, the transition from a glial-to-neuronal cell phenotype appears to promote the progression from neuroendocrine cell hyperplasia to tumor development," the authors wrote. They also found that NETs have higher levels of expression of genes associated with neural stem and progenitor cells, as well as upregulation of factors secreted from neural crest cells that promote neurogenesis and restrict the glial cell fate. Many of these factors are part of the Hedgehog-signaling pathway, and menin is known to repress Hedgehog signaling.

Intestinal glial cells have a high degree of plasticity. They can become neuronal progenitor cells and yet they can dedifferentiate to differentiate again into other cell lineages.

The research could eventually lead to identification of unique cells-of-origin for these tumors. The authors say that the diversity of the tumors – which includes variation in location, mutational profile, and response to therapy – may be due to divergent cellular origins in different tissue sites.

"Defining the cells-of-origin and the events preceding neoplastic transformation will be critical to informing molecular signaling pathways that can then be targeted therapeutically," the authors wrote.

The authors disclosed no conflicts of interest. ■

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