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COURTESY DR. SHAYA NOORIAN/UCLA MEDICAL CENTER

Dr. Shaya Noorian says both metabolic and nonmetabolic factors are likely at play.

NAFLD linked to worse outcomes in IBD

BY JIM KLING
MDedge News

FROM THE CROHN'S & COLITIS CONGRESS

Nonalcoholic fatty liver disease (NAFLD) in patients with inflammatory bowel disease (IBD) is associated with worse outcomes, and that relationship may be influenced by nonmetabolic factors. That is the conclusion of a new nationwide database analysis. NAFLD is common in IBD, with an estimated prevalence of 27%-32%.

Previous smaller studies showed possible links between NAFLD and a history of IBD surgery, IBD disease activity, and metabolic factors, "but none of the studies looked at it on the scale that we did, and our study was more focused on outcomes than simply examining factors associated with both NAFLD and IBD," Shaya Noorian, MD, of UCLA Medical Center in Los Angeles, said in an interview. Dr. Noorian presented the research at the annual congress of the Crohn's & Colitis Foundation and the American Gastroenterological Association.

Dr. Noorian and colleagues found higher rates of hospital readmission, longer hospitalization, and

See **NAFLD** · *page 26*

Defining wellness in IBD goes beyond symptoms

BY JIM KLING
MDedge News

FROM THE CROHN'S & COLITIS CONGRESS

Physicians treating patients with inflammatory bowel disease (IBD) typically focus on disease and symptom management along with quality of life measures, but the latter are not the final word on patient well-being. Social well-being is another outcome that can more accurately portray a patient's satisfaction with their treatment.

That was the message delivered by Laurie Keefer, PhD, AGAF, at a session on diet, stress, health literacy, and disparities in IBD treatment at the annual congress of the Crohn's & Colitis Foundation and the American Gastroenterological Association. "When we talk about disease management, we're talking about these outcomes of mucosal healing, remission, and lack of hospitalizations, but we don't always talk about wellness," said Dr. Keefer, director of psychobehavioral research in the department of gastroenterology at Icahn School of Medicine at Mount Sinai, New York.

Dr. Keefer advocated for incorporating measures that focus on the patient's ability to feel fulfilled,

See **Wellness** · *page 28*

INSIDE

High cost of pancreatic enzymes a barrier for patients with cancer

BY ROXANNE NELSON, RN, BSN

Pancreatic enzyme replacement therapy (PERT) is often an essential component of the treatment regimen for patients with pancreatic cancer, but it can be very pricey.

"Out-of-pocket costs for a 30-day supply of enzymes for Medicare beneficiaries can be as high as $1,000," commented Arjun Gupta, MD, an oncology fellow at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore.

This can contribute to financial toxicity for patients who already have a high symptom burden and

See **Barriers** · *page 22*

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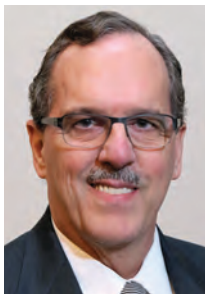
LETTER FROM THE EDITOR

COVID concerns, private equities, and virtual realities

I am hopeful that we are beginning to see a sustained decline in COVID-19 cases and hospitalizations. Although total COVID-19 cases and deaths continue to rise (more than 460,000 deaths in the United States), vaccinations and treatment options have reduced the prevalence of severe disease, hospitalizations, and mortality rates. Worries about variants continue, but we now will enter a prolonged phase before we finally subdue COVID-19 and fully open our economies.

Health systems and practices are looking ahead and beginning to focus on how practice will look after COVID-19. From a business standpoint, we are seeing an accelerating consolidation of community practices. We anticipate the first resale of a private equity (PE)–acquired GI practice: Gastro Health was the first practice to join with a PE firm in 2016. Published rumors suggest a sale of the (now larger, multistate) practice at 15-times-plus EBITDA (earnings before interest, taxes, depreciation, and amortization) could begin as early as this quarter (Oliver E. "For sale – Audax expects to sell Gastro Health in 2021." Becker's GI & Endoscopy. 2021 Feb 8). It would not be a surprise to see 40% of independent gastroenterologists employed in a PE-backed model within a few years. Health systems and payers (especially United Health Group) continue to scoop up practices as well.

Clinical care has been changed forever. I expect fully 30% of visits will remain virtual, and innovative health systems will capitalize on that fact to right-size their brick-and-mortar facilities. Start-up companies will virtualize care and develop new models that allow board-certified gastroenterologists to focus on care they only can provide, resulting in substantial cost savings and (hopefully) similar or better outcomes. Remote patient monitoring (both reactive and predictive) is now firmly entrenched in our care armamentarium.



Dr. Allen

"I expect fully 30% of visits will remain virtual, and innovative health systems will capitalize on that fact to right-size their brick-and-mortar facilities."

As you will see in this issue, we must create more effective interventions for NAFLD. Obesity will play an increasingly important role in the development of digestive and liver disease, so gastroenterologists must develop better tools and processes to combat root causes.

Begin thinking about DDW®. While it again will be a virtual meeting, the content will be rich. Virtual meetings open up additional possibilities to gain new knowledge, although those personal connections over cocktails will be sorely missed.

John I. Allen, MD, MBA, AGAF
Editor in Chief

AGA Community updates

Physicians with difficult patient scenarios regularly bring their questions to the AGA Community (https://community.gastro.org) to seek advice from colleagues about therapy and disease management options, best practices, and diagnoses. The upgraded networking platform now features a newsfeed for difficult patient scenarios and regularly scheduled Roundtable discussions with experts in the field.

In case you missed it, here are some clinical discussions in the newsfeed this month:

- New regulatory perspectives for development of drugs for treatment of NASH (https://community.gastro.org/posts/23673)
- Update on feeding tubes: Indications and troubleshooting complications (https://community.gastro.org/posts/23639)
- Patient case: Hereditary hemorrhagic telangiectasia (HHT) (https://community.gastro.org/posts/23631)
- Patient case: Repeat colonoscopy in a patient with previous negative findings, inadequate documentation (https://community.gastro.org/posts/23630)
- The increasing list of risks associated with PPIs (https://community.gastro.org/posts/23615)
- Patient case: Refractory microscopic colitis (https://community.gastro.org/posts/23604)

View all upcoming Roundtables in the community at https://community.gastro.org/discussions.

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Combo testing improves CRC screening participation

BY WILL PASS
MDedge News

Offering a combination of colonoscopy and fecal immunochemical testing (FIT), either in sequence or by choice, may significantly increase participation in colorectal cancer (CRC) screening, according to a prospective study involving more than 12,000 individuals in Poland.

Still, greater participation did not lead to significantly higher rates of advanced disease detection, reported lead author Nastazja Dagny Pilonis, MD, of the Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, and colleagues in Gastroenterology (2020 Dec 8. doi: 10.1053/j.gastro.2020.11.049).

According to the investigators, screening programs that offer colonoscopy and FIT are more effective than those that offer colonoscopy alone, but an optimal combination protocol has yet to be established, and some parts of the world still rely upon a single diagnostic method.

"In Europe, CRC screening programs often implement only one screening modality: colonoscopy, sigmoidoscopy, or stool testing, depending on the health care provider," the investigators wrote in Gastroenterology. They noted, however, that national guidelines in the United States recommend strategies that include more than one screening method. "'One-size-fits-all' approaches to CRC screening do not result in satisfactory participation" because of behavioral, cultural, and socioeconomic variation among individuals.

To improve understanding of the best ways to improve participation, the investigators conducted a prospective randomized trial, PICCOLINO, via the Polish Colonoscopy Screening Program. In total, 12,485 eligible individuals aged between 55 and 64 years received postal invitations to participate in CRC screening. Individuals were randomized in a 1:1:1 ratio into one of three mailing protocols, each of which involved an initial invitation, and, if needed, a second invitation that offered the following:

- **Control group:** Colonoscopy, with nonresponders receiving the same invitation again
- **Sequential group:** Colonoscopy, with nonresponders or refusers receiving a second invitation that offered FIT
- **Choice group:** Choice between colonoscopy or FIT, with nonresponders receiving the same invitation again

The primary outcome was participation in screening within 18 weeks of enrollment. The secondary outcome was diagnostic yield for either advanced adenoma or CRC.

Out of the three groups, the control group had the lowest participation rate, at 17.5%, compared with

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Epidemiological study explores autoimmune hepatitis rates

BY WILL PASS
MDedge News

The incidence of autoimmune hepatitis (AIH) may be rising, according to a prospective population-based study conducted in New Zealand.

From 2008 to 2016, the rising incidence of AIH led to a 40% increase in point prevalence, reported lead author Mehul Lamba, MD, of Christchurch (New Zealand) Hospital and colleagues.

The present study, which also assessed rates of primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), adds data to an area of inquiry historically characterized by limited and inconsistent results, the investigators wrote in Clinical Gastroenterology and Hepatology (2020 Jun 8. doi: 10.1016/j.cgh.2020.05.061).


Dr. Lamba

They suggested that mixed findings from previous studies may be because of differences in population and environmental factors, but also varying diagnostic criteria.

"The epidemiological trends of these autoimmune liver diseases therefore remain incompletely understood," wrote Dr. Lamba and colleagues.

Their study evaluated trends in autoimmune liver diseases over a 9-year time frame in Canterbury, New Zealand. According to the investigators, this region is well suited to an epidemiological investigation because it is a clearly defined geographic area with approximately 600,000 people, most of whom rely on one tertiary care center: Christchurch Hospital. The bulk of the data therefore came from this center, while a minority of cases were gathered from local private gastroenterology practices, "making complete case ascertainment possible."

Incidence of AIH, PBC, and PSC was assessed at three time points: 2008-2010, 2011-2013, and 2014-2016. AIH had the highest overall incidence, at 1.93 cases per 100,000 people, followed by PSC (0.92) and PBC (0.51).

While the rates of PBC and PSC did not change significantly over time, the incidence of AIH rose from 1.37 cases per 100,000 people in the period of 2008-2010 to 2.39 per 100,000 in 2014-2016 (P = .04), which computes to an incidence rate ratio of 1.69 (95% confidence interval, 1.02-

Continued on following page

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25.8% for the sequential group and 26.5% for the choice group. Multivariable logistic regression showed that individuals in the sequential and choice groups had 64% and 70% higher rates of participation, respectively. Across all groups, age of 60 years or older predicted 12% higher likelihood of participation; in contrast, location more than 40 kilometers from a testing center was associated with an 18% decrease in participation, compared with individuals who lived less than 20 kilometers away.

While the control and sequential groups had similar rates of colonoscopy participation, at 17.5% and 15.9%, respectively (P = .788), this rate was significantly lower, at 8.5%, in the choice group (P = .001). Conversely, the sequential group had a significantly lower rate of FITs than the choice group, at 9.9% versus 17.9%, respectively (P = .001). Among participants with a positive FIT, diagnostic workup colonoscopies were performed in 70.0% of those in the sequential group and 73.3% in the choice group, "despite active call-recall efforts."

Across all invited individuals, advanced disease detection rates were similar across groups, at 1.1% for both the control and the sequential group and 1.2% for the choice group. Among those who were actually screened, the control group had a slightly higher diagnostic yield for advanced neoplasia, at 6.5%, compared with 4.2% in the sequential group and 4.4% in the choice group; however, these differences were not statistically significant. In contrast, significantly more adenomas of any kind were detected in the control and sequential groups (5.6% for both) than the choice group (3.9%) (P < .001).

"Although the strategies which included FIT showed higher participation rates than the strategy of offering colonoscopy alone, these strategies did not result in increased detection rates of advanced neoplasia in the intention to screen analysis," the investigators wrote. "An absolute increase in participation rates of 8%-10% seems insufficient to translate into higher advanced neoplasia detection at the population level."

Dr. Pilonis and colleagues also suggested that the relatively low rate of diagnostic colonoscopy after positive FIT contributed to the suboptimal diagnostic yield.

"These rates are unsatisfactory taking into account significant call-recall efforts, but are within the range reported in other studies," they wrote.

They also wrote that their study compared participation and detection between one-time colonoscopy and one-time screening strategies combining colonoscopy and FIT. In acknowledging this, they noted that these approaches have different screening intervals and uptake over time: "FIT has been shown to achieve higher participation rates than colonoscopy for one time screening, but its uptake over several rounds may not be superior to one time colonoscopy." Furthermore, detection rates of the sequential or choice strategies for advanced disease may rise over time with further implementation, so the one-time screening may not be sufficient to reveal what could become significant differences.

The study was funded by the Polish Ministry of Health, the Polish Foundation of Gastroenterology, and the Centre of Postgraduate Medical Education in Warsaw. FITs, materials, and reagents were provided by Eiken Chemical. The investigators disclosed relationships with Boston Scientific, AbbVie, Olympus, and others.

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Multiple strategies have been validated for CRC screening, showing different characteristics that may affect their acceptability. Indeed, dislike of specific tests has been reported as a barrier to screening for some patients. While adopting more than one method to account for subjects' preferences would then seem a potentially effective approach to increase uptake, most population-based programs are offering only one screening modality.


Dr. Senore

The PICCOLINO study, conducted within the Polish CRC screening program, showed that offering fecal immunochemical tests (FIT) together with colonoscopy, either as an active choice or in sequence, may substantially improve participation as compared with the offer of colonoscopy alone.

The combination approaches offered the opportunity to respond to the screening invitation also to those subjects who prefer a noninvasive test, which may have limited the impact of organizational barriers on participation. Making the test immediately available with the invitation letter likely helped enhance the response rate in the choice group, which may explain the high proportion of subjects opting for FIT. Offering FIT might also reduce disparities related to distance from the endoscopy center seen when using primary colonoscopy screening. A longer follow-up is needed to assess the neoplasia yield of the combination strategies, accounting for the cumulative detection rate of FIT over several rounds.

This study shows that implementing combination approaches within population-based programs represents a feasible option, although the low compliance with referral for colonoscopy assessment would suggest the need to implement communication efforts specifically addressing negative attitudes to colonoscopy among subjects opting for FIT.

Carlo Senore, MD, MSc, is an epidemiologist at the epidemiology and screening unit–CPO at the University Hospital Città della Salute e della Scienza in Turin, Italy; he is the director of Piedmont Region Screening Committee. He has no conflicts.

Nanoparticle encapsulation may unlock HCC therapy

BY WILL PASS
MDedge News

Nanoparticle encapsulation may enable targeting of aberrant glucose metabolism in hepatocellular carcinoma (HCC), potentially amplifying the effects of existing therapies and overcoming resistance mechanisms, according to investigators.

In a preclinical trial involving cell lines, xenograft tumors, and mouse models, encapsulated 2-deoxy-D-glucose (2DG) nanoparticles enhanced the antineoplastic effects of sorafenib and checkpoint inhibitors and suppressed anti-programmed cell death protein 1 (PD1)–resistant tumors, reported lead author Kyo Sasaki, PhD, of Kyushu University in Fukuoka, Japan, and colleagues.

As a glycolysis inhibitor, 2DG acts against the Warburg effect, a cancer immune-resistance mechanism "in which a substantial amount of pyruvate is reduced to lactic acid instead of being directed into mitochondria," the investigators wrote. Their report is in Cellular and Molecular Gastroenterology and Hepatology (2020 Oct 24;11[3]:739-62).

The investigators turned to nanoparticles, which accumulate in tumor tissue more than they do in healthy tissue, thereby limiting off-target toxicity.

But this isn't new information, and Dr. Sasaki and colleagues weren't the first to address the Warburg effect with 2DG; two clinical trials reported signs of efficacy in patients with solid tumors, one in 2010 (Prostate. 2010 Sep 15;70[13]:1388-94) and the other in 2013 (Cancer Chemother Pharmacol. 2013 Feb;71[2]:523-30).

"However, 2DG does not seem to have a significant effect on tumor growth at a dose that does not induce serious adverse effects," wrote Dr. Sasaki and colleagues. "These results suggest a need to develop an efficient drug delivery system for 2DG."

The investigators turned to nanoparticles, which accumulate in tumor tissue more than they do in healthy tissue, thereby limiting off-target toxicity. Specifically, they encapsulated 2DG in nanoparticles of poly(lactic-co-glycolic acid) (PLGA), a Food and Drug Administration–approved biodegradable polymer.

After characterizing the physical properties of the encapsulated 2DG nanoparticles (2DG-PLGA-NPs), and observing tumor localization in nude mice with xenograft liver tumors, the investigators assessed cytotoxic effects.

Treatment resulted in "significant growth reduction" of not only xenograft liver tumors, but also xenograft renal, colon, and pancreatic tumors, "indicating the potential antitumor effects of this method against various tumors." Furthermore, mice treated with encapsulated 2DG nanoparticles had significantly less weight loss compared with those receiving conventional 2DG, suggesting a reduction in 2DG-related adverse effects.

Additional experiments involving two immunocompetent mouse mod-

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2.84). Point prevalence was also significantly higher in 2016, compared with 2008, at 27.5 per 100,000 versus 19.7 per 100,000 ($P < .01$). The investigators described a bimodal age of presentation, with the first peak among patients younger than 20 years, and a second, larger peak among individuals aged 50-69 years.

According to the investigators, the increase in AIH incidence is concordant with the results reported in a Danish study spanning 1994-2012 (J Hepatol. 2014 Mar;60[3]:612-7) and a Dutch study spanning 2000-2010 (Scand J Gastroenterol. 2014 Oct;49[10]:1245-54). They also observed a bimodal distribution of age-incidence consistent with an epidemiological study in Sweden (Scand J Gastroenterol. 2008;43[10]:1232-40), the above-mentioned study from Denmark, and another study from New Zealand (J Gastroenterol Hepatol. 2010 Oct;25[10]:1681-6). The stable levels of PBC and PSC align with two recent retrospective studies conducted in the United States (Clin Gastroenterol Hepatol. 2018 Aug;16[8]:1342-50.e1) and Canada (Hepatology. 2009 Dec;50[6]:1884-92), they added.

"We believe that the observed differential trends in the incidence of these autoimmune liver diseases truly reflects their contemporary epidemiology," the investigators wrote. They went on to suggest that the increase in AIH incidence and prevalence did not stem from an increase in diagnostic scrutiny because the study period did not include any significant changes in gastroenterology service, coding, or diagnostic criteria in the region studied.

"The increased incidence of AIH parallels rising incidence and prevalence of other autoimmune disorders such as [inflammatory bowel disease], type 1 diabetes, and multiple sclerosis in New Zealand, and it is unclear whether these autoimmune conditions share a common local environmental trigger," they wrote. "Environmental factors likely play a central role augmenting phenotypic expression in genetically predisposed individuals."

While Dr. Lamba and colleagues proposed several possible factors, such as increased exposure to pharmaceuticals, definitive factors remain elusive, which the authors cited as one limitation of their study. Another limitation they cited is 35% of AIH cases were classified as "probable" based on established diagnostic criteria since overlapping histological features are observed in drug-induced liver injury and nonalcoholic steatohepatitis. Reassuringly, the diagnosis of AIH was not revised in any of these cases initially classified as "probable" AIH.

"The reason for observed differential change in incidence of these autoimmune liver diseases is unclear," they wrote, "and future collaborative prospective epidemiological study would be required to assess this further."

The investigators reported no conflicts of interest.

ginews@gastro.org

Historically, autoimmune hepatitis (AIH) was a rare disease in reproductive-age women with chronic active hepatitis and autoantibodies. Today with worldwide information available at our fingertips, autoimmune liver diseases such as AIH and variants are in our armamentarium of differential diagnosis for patients with chronic hepatitis. Autoimmune liver conditions are now diagnosed in a wide range of ethnic and age groups.

Dr. Flores

This population-based study in New Zealand by Dr. Lamba and colleagues observed increasing AIH incidence from 2008 to 2016. AIH prevalence was also higher in 2016 versus 2008 (27.5 vs. 19.7 per 100,000). Although more AIH diagnoses were made, advanced fibrosis or cirrhosis was already present in 44.4% at diagnosis without observed differences during the study periods. Liver biopsy, a linchpin in the diagnosis of AIH, was a pitfall in "probable" AIH cases due to overlapping histologic features with drug-induced liver injury and nonalcoholic steatohepatitis.

Unlike highly prevalent chronic liver diseases such as alcohol-related and viral hepatitis, the trigger for AIH in predisposed patients is unknown. It is difficult to explain to susceptible patients how they acquired AIH. In this defined population with centralized access to health care, it would be curious to discover environmental triggers, infections, medications, dietary and gut microbiome changes, or emerging comorbid conditions that influenced the occurrence of AIH. As population studies identified common epidemiologic traits, and when this was combined with serologies and clinical criteria, we became more adept at diagnosis of AIH. Future studies could look at clustering in communities and susceptibility patterns in ethnic groups that may implicate specific etiologic factors.

Avegail Flores, MD, is with the section of gastroenterology and hepatology at Baylor College of Medicine, Houston, and is the medical director of liver transplant at Michael E. DeBakey Houston Veterans Affairs Medical Center. She has nothing to disclose.

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els with multiple large liver tumors added data to support to the relative efficacy of encapsulated versus nonencapsulated 2DG. Both mouse models had significant reductions in liver tumors when treated with 2DG-PLGA-NPs; in contrast, treatment with 2DG alone reduced tumor number in only one of the two mouse models and to a lesser degree than treatment with 2DG nanoparticles.

Further in vivo and ex vivo testing revealed that encapsulated 2DG nanoparticles exerted their cytotoxic effects via endoplasmic reticulum stress, oxidative stress, and inactivation of mTOR. Simultaneously, treatment was associated with CD8+ T-cell migration into tumor tissue via increased glucose uptake and IFN-gamma production in CD8+ T cells, reduced lactate production in tumors, and increased production of CXCL9/CXCL10/CXCL11 in both the tumors and CD8+ T cells.

According to the investigators, these findings suggested that 2DG-PLGA-NPs might upregulate PD-1–positive T cells in tumors, thereby enhancing the effects of a checkpoint inhibitor. Indeed, when syngeneic mice with anti-PD-1–resistant tumors were treated with encapsulated 2DG nanoparticles, the investigators observed significant reductions in tumor growth, compared with treatment using an isotype control, PLGA alone, or an anti-PD-1 antibody. And in nude mice with xenograft tumors, combination therapy with 2DG-PLGA-NPs and sorafenib significantly reduced tumor growth, compared with no treatment, 2DG, PLGA, or PLGA with sorafenib.

"2DG-PLGA-NPs amplified the antitumor effect of anti-PD1 or sorafenib, and showed an antitumor effect against anti-PD1–resistant tumors," the investigators wrote.

Dr. Sasaki and colleagues also noted that encapsulated 2DG nanoparticles did not accumulate in nontumorous cirrhotic hepatocytes, which suggests that treatment would be safe for patients with chronic liver diseases.

"Another practical concern is the extent to which 2DG is effectively taken up by HCC cells," the investigators wrote.

PET showed that the hepatic accumulation rate of F-2-fluoro-2-deoxyglucose (F-FDG), a radioactive tracer of 2DG, was 50% in well-differentiated HCC, and "much higher" in sorafenib-resistant HCC cells and poorly and moderately differentiated HCC cells.

"Thus, 2DG-PLGA-NPs are expected to be good therapeutic agent candidates for patients with advanced HCC," the investigators concluded.

The investigators disclosed no conflicts of interest. Some authors received grants from the Japan Society for the Promotion of Science.

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Treatment of cancer remains a large task, also in the far future. Noninvasive imaging of tumors and thereby potential early diagnosis will very likely be the key for an ever-improving cancer therapy. The so-called Warburg effect of tumors remains a key dogma in oncologic diagnosis: Most tumors consume glucose at a higher rate than normal tissues. However, energetically, this glucose consumption is quite inefficient, and questions remain here. A dogma that maybe never gets "old" was challenged and apparently is revisited here using cutting-edge nanotechnologies.

Dr. Bartneck

Novel avenues appear to get opened by drug encapsulation as presented by Dr. Sasaki and colleagues. Drug encapsulation in general allows at first a very basic principle: protecting the body from the drug, and also the drug from the body. Notably, only drug encapsulation through nanomedicines enables mRNA-based vaccines for the current pandemic. Here, encapsulation has pointed to a way to beat tumors with their own armory and survival mechanism: hitting the glucose metabolism.

Nevertheless, the highly efficient route into the malignant cells is surely worth additional investigation: Which molecular routes are taken by the encapsulated drug here? Do the particles also accumulate in macrophages? If yes, in which, and if not, how can the PLGA formulation overcome the accumulation in macrophages, the "big eaters," that are known to clear vast amounts of nanomaterials from the body?

Matthias Bartneck, PhD, PD, is a group leader specialized in liver immunology at Uniklinik RWTH Aachen (Germany). He has received strong support to develop cell type–specific interventions with tailored drugs for encapsulated nucleic acids, particularly different types of RNA. Dr. Bartneck is actively developing smart nanomedicines to find new cures for liver disease with high unmet need. He has no conflicts.

CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

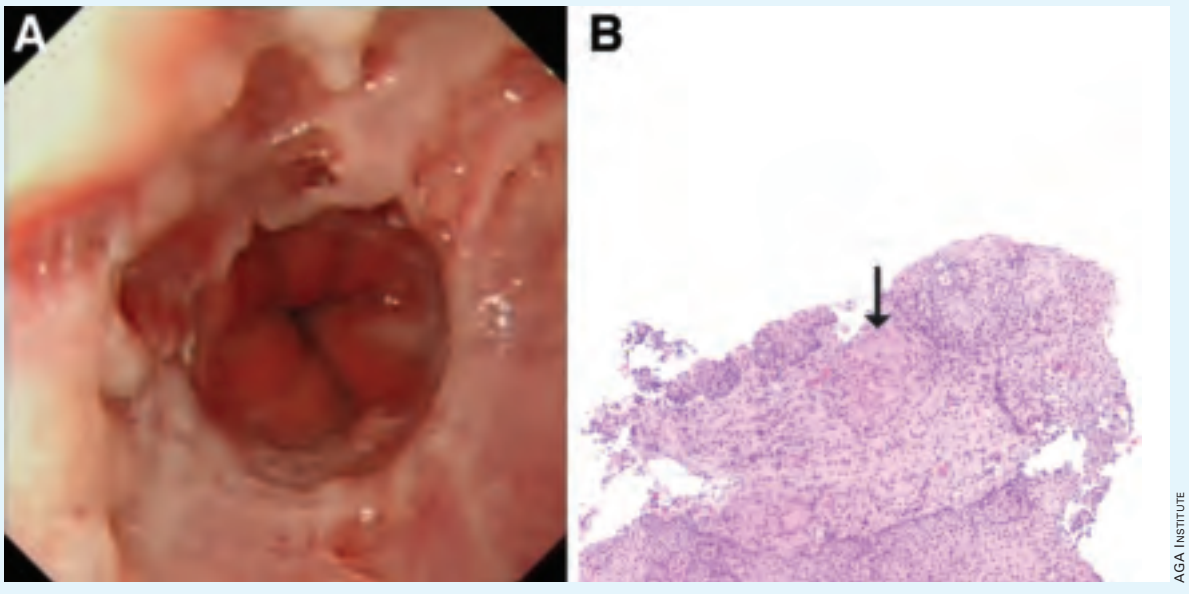
BY THOMAS P. CHAPMAN, DPHIL; RUCHI TANDON, MBBS; AND OLIVER BRAIN, MBBS, MRCP, DPHIL

Published previously in Gastroenterology (2019 Aug 1;157[2]:309-10).

A 49-year-old man presented with symptoms of retrosternal discomfort and mild dysphagia to solids. He had a 30-year history of ileocolonic Crohn's disease requiring previous resections of the ileum and sigmoid colon. Clinical remission had been achieved with adalimumab and azathioprine combination therapy, with the subsequent decision to de-escalate to maintenance with azathioprine monotherapy after consideration of the risks and benefits of dual immunosuppression. After 5 years of azathioprine monotherapy, complete endoscopic remission was reconfirmed at a recent ileocolonoscopy.

To investigate his upper-gastrointestinal symptoms he underwent esophagogastroduodenoscopy that demonstrated severe esophagitis (Los Angeles grade D) of the lower esophagus with biopsies confirming what looked to be reflux esophagitis. However, his symptoms worsened despite a course of high-dose proton pump inhibitor, and a repeat esophagogastroduodenoscopy was performed. This demonstrated deep longitudinal ulcers and inflammation of the lower two-thirds of the esophagus (Figure A). Biopsies were sent for histopathologic analysis (Figure B).

The diagnosis is on page 21.



Advocacy in gastroenterology: Advancing health policies for our patients and our profession

BY ALINE CHARABATY, MD, AGAF, AND NIHAR SHAH, MD, FACP, FACG, FASGE

Physician advocacy is an important tool for health care professionals to protect patients and the vitality of the profession. Medical associations across the spectrum participate in advocacy because of its value in preserving the beneficial role of physicians in health care policy decision-making. This is especially true for specialty physician associations, like the American Gastroenterological Association, which represents more than 9,000 U.S. GI physicians and researchers. Advocacy allows for the voice of GIs and their patients to be heard on Capitol Hill, in the White House, and among various regulatory agencies. When we advocate as a profession, we help ensure good policies gain momentum and halt harmful legislative or regulatory efforts from enactment.

What is physician advocacy?

Physicians are advocating every day for their patients by helping patients make the right decisions about their care. This naturally translates into advocacy at the health policy level. Advocacy is lobbying. While that word may take on a negative meaning for some, it also means being a persuasive communicator, passionate educator, and a leader. National associations, like AGA, often call on members to do just that: educate lawmakers on policies affecting GI, communicate how policies could affect lawmakers' constituencies back in their respective districts, and lead others to support gastroenterology's policy agendas.

Physician advocacy works. AGA had its busiest year for policy work, but this was coupled with a large uptick in GI advocacy engagement. The public health emergency placed many burdens on the health care community and our profession. However, through our advocacy work, we also saw many changes, including increased federal research funding for digestive diseases and GI cancers, passage of legislation to remove patients' barriers to colorectal cancer screening, increased regulatory and reimbursement flexibilities incorporated to ensure physicians could continue to deliver timely care, and creation of federal financial and small-business relief programs to support gastroenterology practices.

COURTESY AGA

AGA's annual Advocacy Day in September 2019 brought more than 45 health care professionals to Capitol Hill to advocate for gastroenterology's policy priorities.

Physician advocacy in GI is especially critical because specialty care is often viewed as having a smaller voice when compared with those of the larger bodies, such as primary care, surgery, or emergency physicians. As a health care specialty with a known shortage across the United States, we need all the help we can get to inform policy makers of our position on controversial policies. In many cases, non–health care professionals are informing policy makers on how to address issues that impact our profession. Additionally, there is a lack of knowledge about health care complexities and needs among decision makers who are ultimately determining how health care is delivered. As health care experts, we are best suited to educate lawmakers on the true impact of health policies. If we do not engage and educate policy makers, our profession and patients will suffer the consequences.

What are GI policy priorities for 2021

AGA will continue its advocacy work in 2021 on the following issues and encourage you and your colleagues to get involved:

Administrative burden relief

Utilization management protocols, like prior authorizations and step therapy, continue to increase and force physicians and their staff to spend hours of extra work time each week to process the paperwork. Prior authorizations are especially troublesome because they have increased for upper-GI procedures and other common procedures. Step therapy protocols have also increased for IBD patients on biologics or other high-cost therapies, resulting in patients not receiving effective therapies as determined by their physician in a timely manner.

Patient access and protections

Coverage

Coverage for patients includes the following two areas:

COVID-19 relief: The public health emergency has weakened the health care workforce with physician practices and researchers facing financial instability and threatened patient access to specialty care. In support of the health care community and as a means to combat the pandemic, the following is necessary: increased access to personal protective equipment

Continued on following page

Meet the 2021 AGA Fellowship inductees

Join the GI community in a round of applause for the 120 members adding the designation "AGAF" in their professional activities. Along with a recognition pin and certificate of acceptance, American Gastroenterological Association President Bishr Omary commends the group in the AGA Community for their superior professional achievements and contributions to the field of gastroenterology.

See the full list and join the discussion at https://community.gastro.org.

Register now for DDW® 2021

Join your colleagues in the digestive disease community at the most prestigious meeting for GI professionals. Registration for Digestive Disease Week® (DDW) 2021 is now open. Register on or before March 31 to receive a discounted rate. AGA member trainees, postdoctoral fellows, medical residents, and students also receive complimentary registration during this early bird period.

In 2021, DDW moves online as a fully virtual meeting, taking place May 21–23, 2021. While DDW Virtual™ will look a little different, we're excited by opportunities the new format provides to learn, share, and connect, such as the following:

- Explore today's most pressing topics and new developments, shared in oral abstract and ePoster presentations.
- Gain the kind of insight that you can't get out of a textbook, presented in sessions led by top GI and hepatology experts.
- Network and build connections with your colleagues in an engaging, interactive setting.

Learn more about DDW and register for your spot at ddw.org.

Continued from previous page

and medical supplies for testing and vaccination distribution and increased rapid tests, testing sites, and health care workers. The public health emergency response also requires a stronger emphasis on health equity given the disproportionate impact it has had on communities of color.

Preserving Affordable Care Act patient protections: The Supreme Court will rule on the Affordable Care Act, a decision which threatens to dismantle the law, including provisions that require insurers to cover preexisting conditions and preventive services. With patients delaying screenings because of the COVID-19 pandemic and the increased incidence among minority and younger populations, it is imperative that preventative screening services – like colorectal cancer screenings – remain fully covered by payers. Moreover, because of the nature of GI diseases, patients often develop multiple conditions throughout their lifetime. The preexisting conditions protections in the ACA ensure that GI patients can gain the insurance coverage they need to obtain quality treatment.

Choice
Health plans and pharmacy benefit managers are using burdensome practices, such as step therapy, to limit patient access to drugs and biologics. These practices disrupt treatment and restrict individuals with digestive diseases from the medicines that work best for them.

Affordability
High out-of-pocket drug and biologics costs limit access to necessary therapies for people with digestive diseases. High out-of-pocket costs contribute to noncompliance, which in turn results in disease progression and complications and increases in overall health care costs.

Research funding
Sustainable long-term funding for federal research is critical to ensure the United States remains a leading contributor to innovative research breakthroughs. Under the current appropriations process in Congress, federal research funding can vary dramatically from year to year. Often enough, research funding for the next fiscal year is delayed by politics in Congress that result in continuing resolutions to fund the government and U.S. research institutions. Unstable funding causes a turbulent environment for investigators and is a deterrent for new investigators entering the field.

Gastroenterologists need to engage in the policymaking process as there are too many threats and opportunities in today's policy arena.

Member engagement
GIs need to engage in the policymaking process as there are too many threats and opportunities in today's policy arena. The effectiveness of AGA's advocacy work in the federal government is contingent upon members' engagement in public policy. To increase physician advocacy and AGA member engagement, AGA offers the following avenues for members:

AGA political action committee
Political engagement is a powerful tool physician advocates can use to increase the visibility of GI on Capitol Hill. Political action committees (PACs) help provide access to lawmakers and their staff so that our advocates can educate them on the rationale for supporting our clinical and research priorities. Although PACs do not guarantee successes in Congress, it is important to note that contributions to legislators' campaigns help them to be run more smoothly and effectively and allow the legislators to continue to serve their constituents. AGA PAC is a bipartisan political arm of AGA and is the only PAC dedicated to gastroenterology. Learn more at gastro.org/AGA-PAC.

Grassroots engagement
Build a relationship with your elected officials and their health policy staff by communicating with them often and offering to serve as a resource to the office on issues related to specialty medicine. AGA makes this easy with its online advocacy action center: gastro.quorum.us. Find out who your lawmakers are and research their background, engage them by email or Twitter on priority policy issues, and share stories with AGA staff about your interactions with congressional offices.

Congressional Advocates Program
This program creates a national grassroots network of engaged gastroenterologists interested in advocating for our profession and patients. Congressional Advocates are mentored and receive year-round advocacy training by AGA leadership and staff. Learn more at gastro.org/advocacy-and-policy/congressional-advocates-program.

How can you start advocating for gastroenterology?
A new session of Congress has just begun, a new administration with a heavy health care agenda was elected into office, and gastroenterology needs your voice more than ever as we advocate for what really matters to us and our patients. Join your colleagues at AGA's spring virtual Advocacy Day on April 22, 2021. The event allows AGA members to meet with lawmakers and health policy staff virtually to educate them on the priority issues affecting our profession. AGA staff makes it easy for you to participate. Webinar trainings, meeting schedules, and talking points will be provided to you ahead of time. For this event, we will speak to lawmakers about increasing federal research funding, addressing regulatory burdens like prior authorizations and step therapy protocols, and ensuring gastroenterologists and investigators have continued support during the COVID-19 pandemic.

For more information, visit gastro.org/aga-advocacy-day or contact AGA's senior public policy coordinator, Jonathan Sollish, at jsollish@gastro.org.

Giving stock to the AGA Research Foundation can be a win-win

If you own stock that's increased in value since you purchased it (and you've owned it for at least 1 year), you have a unique opportunity for philanthropy. When you donate securities to the AGA Research Foundation, you receive the same income tax savings (if you itemize) that you would if you wrote the AGA Research Foundation a check, but with the added benefit of eliminating capital gains taxes on the transfer, which can be as high as 20%.

Making a gift of securities to support the AGA Research Foundation's mission to raise funds to support young researchers in gastroenterology and hepatology is as easy as instructing your broker to transfer the shares. Using assets other than cash also allows you more flexibility when planning your gift.

Benefits:
- Receive an income tax deduction for gifts of securities if you itemize.
- Provide relief from capital gains tax with gifts of securities.
- Help fulfill our mission with your contribution.

Take the next step
The AGA Research Foundation can help clarify and document the steps to donate stock to us. Contact us at foundation@gastro.org to make your donation.

This year's Recognition Prize recipients

AGA has announced the 2021 recipients of its annual recognition prizes, given in honor of outstanding contributions and achievements in gastroenterology.

"AGA Recognition Prizes allow members to honor their contemporaries for their exceptional contributions to the field of gastroenterology and hepatology," said Hashem B. El-Serag, MD, MPH, AGAF, chair of AGA.

"The 2021 AGA Recognition Prize winners represent only a small group of our widely distinguished and exceptional members who help make AGA such an accomplished organization. We are honored that such esteemed individuals are representatives of AGA."

This year the AGA Recognition Prizes will be presented virtually in May 2021.

To learn more about our 2021 AGA recognition prize recipients, visit https://gastro.org/2021awards.

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GI & HEPATOLOGY NEWS
THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

PRACTICE MANAGEMENT TOOLBOX

Important lessons about telehealth

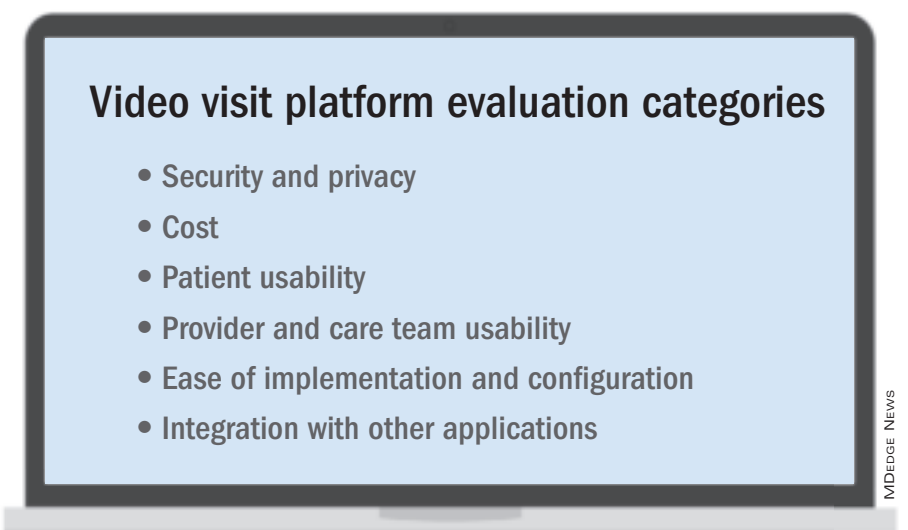
BY AMY N. WINKELMAN

Telehealth exploded into the public consciousness in 2020 as a way for clinicians and patients to safely connect during the COVID-19 crisis. While telehealth has been part of care delivery at Providence St. Joseph Health (PSJH) for more than a decade, it transitioned almost overnight from an offering most often focused on serving patients in rural areas to a way for any patient to get the care they need virtually whether in a hospital, outpatient facility, or from the comfort and safety of their own home.

The recent growth seen in telehealth was fueled by changes in regulation and reimbursement during the COVID-19 public health emergency that enabled providers to see new and established patients at home across all payer types. For perspective, the large PSJH system averaged a few thousand video visits per month in January and February 2020. As SARS-CoV-2 transmission spread and lockdowns began, that number climbed to over 15,000 video visits in March to a height of more than 150,000 video visits in May. As of the end of October 2020, PSJH has conducted more than 1.2 million video visits since the beginning of January, steadily accounting for 20%-25% of total visit volume.

Going virtual with gastroenterology

Gastroenterology providers have been a part of this wave at PSJH:



They have conducted more than 12,000 video visits by the end of 2020 (as documented in our Epic EMR), which has been an entirely new method of care delivery for most of these clinicians. We also have many affiliated, private practice gastroenterology providers who practice in our facilities and transitioned quickly to video for outpatient care.

Pre- and postprocedure follow-up visits were some of the most common types of visits to become virtual this past year, along with new patient visits for establishing care and visits for existing patients for check-ins on the status of a health condition, medication, or other concern.

In addition, complementary services for gastroenterology patients were transitioned to video over the past several months. With these transitions, care management, nutrition services, online support groups, bariatric care information sessions, behavioral health, and more are now available for patients to access virtually.

Remembering it's not about the tech

New technologies can be challenging to adopt – especially at a pace as rapid as it was in 2020. Fortunately for PSJH, we had inpatient and outpatient video platforms already in place and an experienced internal telehealth team to scale them quickly to providers and caregivers across system. But even with those advantages, it was still a huge challenge to transition so many providers and caregivers to video visits in such a short time without change-management hurdles and bumps along the way.

Too often, there is an overemphasis placed on the technology. It's a tool, and some technologies are better than others, and they continue to evolve over time. True success or failure lies in the clinical and operational workflows and how well the providers and care teams engage with and adapt them. We found that the providers and staff members willing to venture outside their comfort zone of "how we've always done it" and collaborate on the transition to virtual care had the best results. Openness and flexibility to trying new things and using temporary workarounds if existing functionality didn't meet the need was key to transitioning quickly. Then, by listening to ideas from and sharing feedback among providers, clinics, and geographies, we were able to identify fixes and optimizations that needed to be made to improve the experience for all.

Selecting a video visit platform

No telehealth platform is perfect and meets every patient, provider, and staff need or request despite what a technology vendor may claim. This is especially true in a large and/or diverse system with many different types of clinical use cases. Determining the "must-have" requirements from among those that may be important or simply nice to have is critical when selecting the video visit platform to use.

It's not an easy decision, and it's nearly impossible to please everyone. It is essential to ensure that there are clinician, operator, and technical stakeholders all contributing to the requirements and decision-making. While some

Continued on following page

Should patients be tested for COVID before endoscopy?

Reassurance is important to both patients and providers

According to a rapid review and guideline from the American Gastroenterological Association (Gastroenterology. 2020 Nov;159[5]:1935-48.e5), testing can help decrease the risk of transmission by triage (delaying the procedure) of patients with positive tests who could infect other patients and health care workers. In addition, for patients with negative tests, surgical masks can be considered during endoscopy to allow preservation of N95/N99 masks that are a limited resource in many settings. Varying strategies for reopening endoscopy have been adopted by endoscopy centers and health systems. According to one survey, 52% of responding U.S. endoscopy centers performed testing on all patients prior to endoscopy, which highlights the large variation of policies in clinical practice (Gastroenterology. 2020 Oct 1;159[4]:1568-70.e5). In the case for a strategy of pretesting all patients prior to endoscopy, it's important to emphasize that the benefits of testing outweigh any downsides and that, for health care professionals and patients alike, providing reassurance about the safety of endoscopy for everyone is an important aspect to resuming endoscopy operations.

Dr. Inadomi

John M. Inadomi, MD, AGAF, is with the department of medicine at the University of Utah, Salt Lake City. He has no conflicts to declare.

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

Barriers to care should be avoided

Indeed, the aftermath of this COVID pandemic will be far reaching. While telemedicine has helped mitigate some of the collateral damage, the disruption of cancer screening and surveillance programs may lead to high cancer-related morbidity and mortality. In one study evaluating the impact of COVID-19 on the U.S. cancer population (JCO Clin Cancer Inform. 2020 Nov;4:1059-71), authors analyzed 6,227,474 Medicare Fee For Service claims (representing 5%-7% of the Medicare population) and found a substantial decrease in cancer screening and cancer care (therapy and surgeries).

Dr. Sultan

At the peak of the pandemic in April, screening for colon cancer was reduced by 75%. Eliminating any potential barriers to care should be the highest priority. A requirement for patients to undergo preprocedure testing may contribute to increased anxiety and added costs and may further delay care. From a patient perspective, finding a testing facility, obtaining the test within 48-72 hours, self-isolating until the day of endoscopy, and dealing with the uncertainty of the test result may serve as additional barriers for completion of endoscopy. Moreover, the differential availability of testing may further exacerbate health inequities.

Shahnaz Sultan, MD, MHSc, AGAF, FACG, is with the division of gastroenterology at the University of Minnesota in Minneapolis and the Center for Care Delivery and Outcomes Research at Minneapolis Veterans Affairs Healthcare System. She has no conflicts to declare.

Dear colleagues and friends,

Dr. Kahi

Welcome to another edition of the Perspectives debates. The COVID-19 crisis has directly affected our endoscopy practices, and it's raised difficult questions about how best to balance safety with continued delivery of health care services. Dr. John M. Inadomi and Dr. Shahnaz Sultan address the benefits and downsides of universal testing of patients before endoscopic procedures. I hope you find this debate helpful and informative for your endoscopy unit policies as we navigate these uncertain times. As always, I welcome your comments and suggestions for future topics at ginews@gastro.org. Stay safe!

Charles J. Kahi, MD, MS, AGAF, is a professor of medicine at Indiana University, Indianapolis. He is also an associate editor for GI & Hepatology News.

Continued from previous page

stakeholders may prefer a "best-of-breed" solution that does one thing very well, it may have to be paired with a set of other complementary applications to meet all of the organization's needs. Alternatively, there may be a platform with an expansive feature set but not all of the features are as strong as desired. Then there are solutions that integrate with your existing applications, which is usually a compelling option to consider.

Regardless of the tool chosen, best-practice workflows, easy-to-follow documentation, a mix of different training options, and internal technical help that responds quickly is key to implementing it successfully. And once implemented, optimization is an ongoing process to make it easier, faster, and better.

Looking ahead

As we came to the end of 2020, most providers and health systems were paying close attention to the Centers for Medicaid & Medicare Services and state-level regulations and reimbursement changes for 2021 to evaluate the impact on telehealth after the public health emergency and COVID-19 waivers are ended. Advocacy efforts are urging lawmakers to not lose the gains that were made during this time and have enabled millions of patients to access care more easily – changes which we believe they will now expect as an option going forward.

We found that the providers and staff members willing to venture outside their comfort zone of "how we've always done it" and collaborate on the transition to virtual care had the best results.

We at Providence believe telehealth's future is a bright one, especially where value-based/managed care arrangements with payers are in place. In addition to integrating video visits and consults into normal clinical practice, we see further growth in serving patients at home with remote patient monitoring and other home-based programs that leverage connected devices and virtual tools.

We also anticipate more providers will acquire licenses in other states to virtually care for patients who lack access to specialty services in their own community, which increases access where it is most needed.

After 2020, we hope that telehealth will no longer be a specialized service only some patients can receive but a normal way of delivering care to all.

Ms. Winkelman is the system director of telehealth product development and delivery at Providence St. Joseph Health. Providence is the third-largest nonprofit health system in the United States with 51 hospitals, more than 800 clinics, and a comprehensive range of health and social services across Alaska, California, Montana, New Mexico, Oregon, Texas, and Washington. She has reported no conflicts.

AGA Clinical Practice Update

Bariatric surgery in patients with cirrhosis

BY AMY KARON
MDedge News

Obesity, a risk factor for nonalcoholic fatty liver disease (NAFLD) and a prevalent comorbidity among people with cirrhosis of all etiologies, is associated with a number of untoward health outcomes, and weight loss is an important goal, according to a clinical practice update from the American Gastroenterological Association. According to one study (Hepatology. 2011 Aug;54[2]:555-61) cited in the update, approximately 30% of patients with cirrhosis have comorbid obesity, and this figure may increase even further as the epidemic of NAFLD progresses.

For obese patients with cirrhosis, weight loss "is an important therapeutic goal" because obesity heightens risks of portal vein thrombosis, portal hypertension, hepatocellular carcinoma, liver failure in acute on chronic liver disease, and other concerns. Despite no longer being an absolute contraindication, obesity can also complicate liver transplantation considerations, Heather Patton, MD, AGAF, of the Veterans Affairs San Diego Healthcare System and associates wrote in Clinical Gastroenterology and Hepatology (2020 Oct 22. doi: 10.1016/j.cgh.2020.10.034). Consideration of individuals with cirrhosis, however, requires careful scrutiny of surgical candidacy, appropriate resources for care of patients with advanced liver disease, and a high-volume bariatric surgical center given the inherent risks of surgical procedures in this patient population.

For patients with cirrhosis and obesity, laparoscopic sleeve gastrectomy is probably the best option for bariatric surgery because it preserves endoscopic access to the biliary tree, facilitates gradual weight loss, and does not cause malabsorption, according to the update.

For obese patients with cirrhosis, weight loss "is an important therapeutic goal" because obesity heightens risks.

Clinicians and patients should time bariatric surgery based on liver disease stage – for patients with decompensated disease, surgery should be performed only at the same time as or after liver transplantation, the experts wrote. Clinicians should also evaluate candidacy for liver transplantation before bariatric surgery "so that patients who are ineligible for transplant (and their families) have a clear understanding of this, avoiding the need for the medical team to address this issue urgently if the patient's condition deteriorates postoperatively."

One review suggested that bariatric surgery is "the most effective and durable" means of weight loss (JAMA Surg. 2014 Mar;149[3]:275-87), according to the authors of the update; however, another review suggested increased surgical risk for bariatric surgery among patients with cirrhosis (Clin Gastroenterol Hepatol. 2019 Mar;17[4]:595-606), so the update's authors advised individualized risk-benefit assessments. These assessments are made even more complicated by scarcity of relevant randomized trial data, so the experts identified PubMed-indexed, peer-reviewed articles published between 2000 and 2020 and used these to make 10 best practice advice statements for bariatric surgery in obese patients with cirrhosis.

The surgical, anesthesia, and medical teams must be well versed in assessing and operating on patients with portal hypertension and cirrhosis and in managing these patients postoperatively, the experts wrote. The preoperative assessment should include cirrhosis status (compensated versus decompensated); the presence and severity of sarcopenia, ascites, and portal hypertension; and candidacy for liver transplantation. It is vital to check for clinically significant portal hypertension (CSPH) because endoscopic devices should not be used in patients with gastric and/or esophageal varices. To do so, upper endoscopy and cross-sectional imaging are advised, pending better data on noninvasive assessment methods. For patients without CSPH, endoscopic bariatric treatment can be somewhat less effective for weight loss but also might be less likely to lead to postoperative complications. However, head-to-head and long-term safety data are not yet available.

The experts also noted that bariatric surgery increases the effects (blood levels) of alcohol and can increase the risk of developing an alcohol use disorder. Clinicians should carefully take the history of alcohol use and repeatedly educate patients about the risks of consuming alcohol after bariatric surgery. According to a study from 2012 (JAMA. 2012 Jun 20;307[23]:2516-25) and a review from 2015 (Alcohol Clin Exp Res. 2015 Sep;39[9]:1582-601), male sex, younger age, less social support, and regular or "problematic" alcohol use before bariatric surgery heighten the risk for developing an alcohol use disorder afterward.

Funding sources included the Robert H. Yauk Charitable Trust Gift for Liver Transplant Research 2017-2020 and Regenerative Medicine for Prevention of Post-Transplant Biliary Complications. The authors reported having no conflicts of interest.

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Eliminating hepatitis by 2030: HHS releases new strategic plan

BY MARK S. LESNEY, PHD
MDedge News

In an effort to counteract alarming trends in rising hepatitis infections, the U.S. Department of Health & Human Services has developed and released its Viral Hepatitis National Strategic Plan 2021-2025, which aims to eliminate viral hepatitis infection in the United States by 2030.

An estimated 3.3 million people in the United States were chronically infected with hepatitis B virus (HBV) and hepatitis C virus (HCV) as of 2016. In addition, the country "is currently facing unprecedented hepatitis A virus [HAV] outbreaks, while progress in preventing hepatitis B has stalled, and hepatitis C rates nearly tripled from 2011 to 2018," according to the HHS.

The new plan, "A Roadmap to Elimination for the United States," builds upon previous initiatives the HHS has made to tackle the diseases and was coordinated by the Office of the Assistant Secretary for Health through the Office of Infectious Disease and HIV/AIDS Policy.

The plan focuses on HAV, HBV, and HCV, which have the largest impact on the health of the nation, according to the HHS. The plan addresses populations with the highest burden of viral hepatitis based on nationwide data so that resources can be focused there to achieve the greatest impact. Persons who inject drugs are a priority population for all three hepatitis viruses. HAV efforts will include a focus on the homeless population. HBV efforts will also focus on Asian and Pacific Islander and the Black, non-Hispanic populations, while HCV efforts will include a focus on Black, non-Hispanic people, people born during 1945-1965, people with HIV, and the American Indian/Alaska Native population.

There are five main goals outlined in the plan, according to the HHS:

- Prevent new hepatitis infections.
- Improve hepatitis-related health outcomes of people with viral hepatitis.
- Reduce hepatitis-related disparities and health inequities.
- Improve hepatitis surveillance and data use.
- Achieve integrated, coordinated efforts that address the viral hepatitis epidemics among all partners and stakeholders.

"The United States will be a place where new viral hepatitis infections are prevented, every person knows their status, and every person with viral hepatitis has high-quality health care and treatment and lives free from stigma and discrimination. This vision includes all people, regardless of age, sex, gender identity, sexual orientation, race, ethnicity, religion, disability, geographic location, or socioeconomic circumstance," according to the HHS vision statement.

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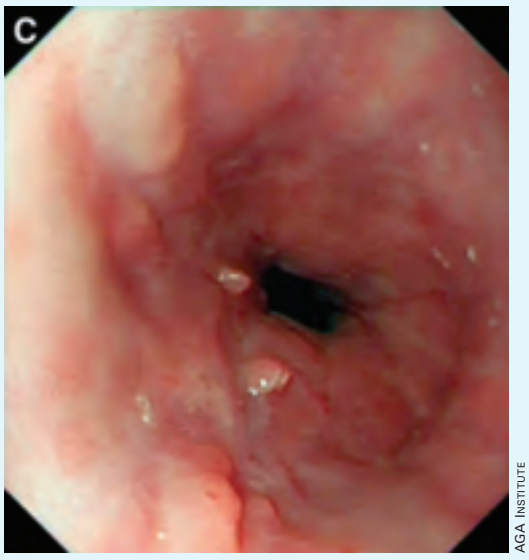
The diagnosis

Answer to "What is your diagnosis?" on page 8: Esophageal Crohn's disease.

The esophageal biopsies demonstrate severe chronic inflammation of the subepithelial tissue with marked lymphocytic infiltration and the presence of granulomas containing multinucleate giant cells (Figure B, arrow). Given his immunosuppression with azathioprine, stains for cytomegalovirus, herpes simplex virus, and mycobacterial and fungal organisms were performed and returned negative.

A diagnosis of esophageal Crohn's disease was made, and adalimumab was recommenced. A rapid and dramatic clinical improvement was observed, with complete resolution of his symptoms. Adalimumab trough levels were checked and found to be therapeutic (9 mcg/mL). Repeat esophagogastroduodenoscopy at 6 months showed healing of the esophageal ulceration, with residual scarring and the presence of two postinflammatory polyps (Figure C). The histopathology was consistent with quiescent Crohn's disease.



AGA Institute

Recognition of this very rare manifestation of Crohn's is challenging but important so that appropriate treatment is not delayed. It is both unexplained and unusual for Crohn's disease to flare in a new gastrointestinal location. Moreover, although accurate adult prevalence data for esophageal Crohn's are scarce, retrospective data suggest it is present in just 0.2% of Crohn's disease patients.[1] By contrast, gastroesophageal reflux disease prevalence is between 18% and 28% of the total population in North America. Esophageal Crohn's commonly leads to nonspecific symptoms that resemble gastroesophageal reflux disease, and as for acid reflux, the mid and distal esophagus are the most common sites of involvement. In keeping with the behavior of luminal Crohn's disease, progression from inflammation to stenosis (causing marked dysphagia) or perforation (leading to fistula formation) may occur.[2] Histopathology typically demonstrates chronic inflammation, although noncaseating granulomas are seen in the minority (7%-39%) of patients.[3] Multiple deep biopsies are recommended to improve diagnostic yield,[3] and our case demonstrates the value of repeat endoscopic evaluation.

Unsurprisingly given its rarity, there are no systematic data on optimal treatment. Acid suppression therapy may provide symptomatic benefit but does not treat the underlying inflammatory process. Oral prednisolone, topical budesonide, and immunomodulators including thiopurines have been used in case series, but biological therapy (typically anti–tumor necrosis factor therapy) is likely to be required for severe disease.[2,3] There are no data on the use of more novel biologics. Critically, almost all reported cases of esophageal Crohn's disease have concomitant intestinal disease, and the presence of upper gastrointestinal Crohn's predicts a more severe disease phenotype, supporting the use of more aggressive medical therapy in this instance.[3]

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Patients could face costs of $1,500 a month

Barriers *from page 1*

distress. The high cost of this supportive care has been underappreciated, he said.

In addition to its use for patients with pancreatic cancer, PERT is also prescribed to patients with chronic pancreatitis and cystic fibrosis. These enzymes can reduce symptoms of indigestion and improve nutrition for patients with exocrine pancreatic insufficiency, he explained.

"Out-of-pocket costs for two large pancreas enzyme capsules, which are often required for a meal, may be $15. And these need to be taken at every meal and may be more expensive than the meal itself," he said in an interview.

Dr. Gupta led a new study that showed that, among Medicare beneficiaries, the expected out-of-pocket costs for a 30-day supply of optimally dosed PERT averaged $999 across formulations. Patients' costs, including deductibles and coinsurance, ranged from $853 to $1,536.

The out-of-pocket costs were lower after patients met the deductible ($673; range, $527-$1,210) and continued to decrease after reaching catastrophic coverage ($135; range, $105-$242). The findings were presented at the 2021 Gastrointestinal Cancers Symposium.

Dr. Gupta noted that there has been a lot of publicity about very expensive anticancer drugs, but little has been said about the costs of products used in supportive care. "While it's true that many patients cannot afford the drugs, there are patient-assistance programs where they can often get them free of charge," he said. "But supportive care agents, such as those for constipation or the enzymes – all of those can nickel and dime you and end up being very costly."

These agents add substantially to the drug cost burden. "Some patients also need insulin, which is also insanely expensive," he said.

One of the reasons for the high cost of PERT is that there are very few options, and all the available products are brand-name agents. Dr. Gupta noted that clinicians often underprescribe pancreatic enzymes in clinical practice. "Because of this, we wanted to look at what are the estimated out-of-pocket costs for patients directly when they're prescribed an optimal regimen of pancreatic enzymes," he said.

In addition to its use for patients with pancreatic cancer, pancreatic enzyme replacement therapy is also prescribed to patients with chronic pancreatitis and cystic fibrosis.

Study details

For their study, Dr. Gupta and colleagues assessed PERT costs using the Medicare Part D formulary and pricing files for the first quarter of 2020. Point-of-sale and out-of-pocket costs for each PERT formulation were calculated among Part D standalone and Medicare Advantage prescription drug plans.

Costs were then assessed using three scenarios: the standard-benefit design, with a $435 deductible and 25% coinsurance after the deductible is met; 25% coinsurance to fill a prescription after the deductible while in the coverage gap until the patient spends $6,350 out of pocket; and 5% coinsurance once catastrophic coverage is reached.

Across 3,974 plans nationwide, four formulations in 17 different doses were covered by Medicare plans during the study period. Doses ranged from 3,000 to 40,000 lipase units, and the per-unit list price ranged from $1.44 to $13.89. The point-of-sale price for a 30-day supply of optimally dosed PERT ranged from $2,109 to $4,840.

Dr. Gupta noted that a "good-sized meal often requires 80,000 units of lipase, or two of the very largest pills. Of note, these pills need to be taken meal after meal every meal throughout a patient's life."

Prescribers and dietitians try to find the least expensive options, including patient-assistance programs, but in the end, they are sometimes forced to underprescribe. "Some patients will go and buy over-the-counter pancreatic enzyme supplements, and it seems like a good way to cut costs," said Dr. Gupta, "but it is not recommended for people with pancreatic cancer."

The problem with these formulations is that they are not regulated. "The enzyme content in them is also minuscule, in the range of hundreds of units instead of the 50,000 units needed per meal," he said. "Patients end up spending much more for ineffective therapies."

The study received no outside funding. Dr. Gupta disclosed no relevant financial relationships.

A version of this article first appeared on Medscape.com.

Pancreatic cyst test could help rule out cancer, surgery

BY SUSAN LONDON
MDedge News

A test that uses machine learning may improve the management of patients with pancreatic cysts, sparing some of them unnecessary surgery, a cohort study suggests.


Dr. Karchin

Rachel Karchin, PhD, of Johns Hopkins Whiting School of Engineering in Baltimore, reported these results at the AACR Virtual Special Conference: Artificial Intelligence, Diagnosis, and Imaging (Abstract IA-13).

"Preoperative diagnosis of pancreatic cysts and managing patients who present with a cyst are a clinical conundrum because pancreatic cancer is so deadly, while the decision to surgically resect a cyst is complicated by the danger of the surgery, which has high morbidity and mortality," Dr. Karchin explained.

She and her colleagues applied machine learning to this classification challenge, using data from 862 patients who had undergone resection of pancreatic cysts at 16 centers in the United States, Europe, and Asia. All patients had a known cyst histopathology, which served as the gold standard, and a known clinical management strategy (discharge, operate, or monitor).

The investigators used a multivariate organization of combinatorial alterations algorithm that integrates clinical features, imaging characteristics, cyst fluid genetics, and serum biomarkers to create classifiers.

The resulting test, CompCyst, was trained using data from 436 of the patients and then validated in the remaining 426 patients. In the validation cohort, for classifying patients who should be discharged from care, the test had a sensitivity of 46% and a specificity of 100%, according to results reported at the conference and published previously (Sci Transl Med. 2019 Jul 19. doi: 10.1126/scitranslmed.aav4772). For immediately operating, CompCyst had a sensitivity of 91% and a specificity of 54%. And for monitoring the patient, the test had a sensitivity of 99% and a specificity of 30%.

When CompCyst was compared against the standard of care based on conventional clinical and imaging criteria alone, the former was more accurate. CompCyst correctly identified larger shares of patients who should have been discharged (60% vs. 19%) and who should have been monitored (49% vs. 34%), and the test identified a similar share of patients who should have immediately had an operation (91% vs. 89%).

"The takeaway from this is that standard of care is sending too many patients unnecessarily to surgery," Dr. Karchin commented. "The CompCyst test, with application of the three classifiers sequentially – discharge, operate, or monitor – could reduce unnecessary surgery by 60% or more based on our calculations."

AGA Resource
Help your patients understand pancreatitis testing and treatment options, symptoms, and complications by sharing AGA's patient education from the GI Patient Center: www.gastro.org/pancreatitis.

Dr. Karchin disclosed no conflicts of interest. The study was supported by the Lustgarten Foundation for Pancreatic Cancer Research, the Virginia and D.K. Ludwig Fund for Cancer Research, the Sol Goldman Pancreatic Cancer Research Center, the Michael Rolfe Pancreatic Cancer Research Foundation, the Benjamin Baker Scholarship, and the National Institutes of Health.

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Registry reveals *H. pylori* management mistakes

BY WILL PASS
MDedge News

Many patients are receiving inadequate eradication therapy for *Helicobacter pylori* infection, according to analysis of a European registry.

Olga P. Nyssen, BSc, PhD, of the Autonomous University of Madrid and colleagues discussed seven errors in their analysis, published in the Journal of Clinical Gastroenterology (2021 Jan 5. doi: 10.1097/MCG.0000000000001482), which included prescribing a triple instead of quadruple regimen, prescribing therapy for too short of a duration, and prescribing a low dose of proton pump inhibitors (PPIs).

The European Registry of *H. pylori* Management (Hp-EuReg) "represents a good mapping overview of the current situation regarding *H. pylori* management, allowing not only continuous assessment of the integration of clinical recommendations agreed on medical consensus, but also of the possible strategies for improvement."

Patient data were drawn from registry-participating countries that each had more than 1,000 cases of *H. pylori* available; most came from Spain, followed by Russia, Italy, Slovenia, and Lithuania. Of these patients, data for 26,340 patients were analyzed, which ultimately represented 80% of the total registry from 2013 to 2019.

The first mistake discussed in the paper regarded use of less-effective triple therapies (typically PPI plus two antibiotics); one review showed that these regimens fail in 20%-40% of cases (Aliment Pharmacol Ther. 2011 Dec;34[11-1]:1255-68). Increasing antibiotic resistances have only worsened the success rate. According to the current study, a triple regimen was given as first-line treatment in 46% of cases. Overall, frequency of triple-therapy prescriptions decreased from higher than 50% in 2013 to about 40% in 2019. More significant improvements in this area were achieved in Spain, where use of triple therapies decreased from 24% in 2014 to 0% in 2019.

The authors pointed out that "overwhelming evidence" supports 14-day treatment; however, 69% of triple-therapy durations and 58% of quadruple-therapy durations were for only 7 or 10 days. Triple therapy at this duration showed only 81% cure rate, while it was 88% with 14 days, and quadruple therapy was only 80% effective at 7-10 days but 90% effective at 14 days. "Fortunately," the investigators wrote, "this mistake was progressively found less frequently and, at present, the prescription of 7-day standard triple therapy regimens has almost disappeared."

The authors noted acid suppression via PPIs improves cure rates: In one meta-analysis (Aliment Pharmacol Ther. 2008 Oct 1;28[7]:868-

Continued on following page

Color-imaging endoscopy improves neoplasm detection

BY M. ALEXANDER OTTO

Use of linked-color imaging for upper-gastrointestinal tract endoscopy improves the detection of neoplasms in comparison with conventional white-light imaging, according to results from a randomized trial involving more than 1,500 patients.

Linked-color imaging (LCI) is an advanced illumination technique that combines white light with narrow-band short-wavelength light to enhance the contrast of red and white hues during endoscopy, making it easier to recognize subtle differences in mucosal color.

At present, LCI is available only on systems manufactured by Fujifilm (that is, the Lasereo endoscopic system marketed in Japan and the Eluxeo system in the United States and Europe). The system includes the light source and a processor and can be used with various endoscopes.

"Combined with previous studies that show the efficacy of LCI in detecting large intestinal neoplasia, our findings make a strong case for wider adoption of this modality in surveillance of the entire endoscopically accessible digestive tract," senior investigator and gastroenterologist Mototsugu Kato, MD, of the Hakodate National Hospital, Hokkaido, Japan, said in a press release.

The randomized trial was conducted at 19 Japanese hospitals by 58 expert endoscopists, all of whom were experienced with LCI.

"We need further research to confirm [LCI's] efficacy in the hands of general clinicians for upper GI screening" of an average-risk population, Dr. Kato said.

Results from the trial were published in Annals of Internal Medicine (2020 Oct 20. doi: 10.7326/M19-2561).

Approached for comment, gastroenterologist Marvin Ryou, MD, director of endoscopic innovation at Brigham and Women's Hospital, Boston, said that he has used Fujifilm's LCI technology mostly for polyp detection on colonoscopy and has found it useful.

Linked-color imaging is an advanced illumination technique that combines white light with narrow-band short-wavelength light.

LCI "has been shown to be helpful for the detection of colonic neoplasia, and this Japanese multicenter study provides additional evidence of utility in foregut neoplasm detection. I would look forward to future studies of LCI in an average-risk population," he said.

Details of the randomized trial

All of the trial participants had previous or current gastrointestinal cancer and were undergoing upper-GI endoscopic surveillance. Patients were a little older than 70 years on average, and more than 75% were men.

The patients underwent two examinations during their endoscopy sessions, one performed with LCI, and the other with conventional white-light imaging (WLI). The endoscopy system used in the study allowed the scope to switch between the two modalities, as well as others.

Overall, 750 patients were randomly assigned to undergo LCI first and then WLI; 752 underwent WLI first and then LCI.

In both groups, lesions were most common in the stomach, followed by the esophagus and the pharynx.

Neoplastic lesions in the pharynx, esophagus, or stomach – confirmed by histology – were detected in 60 patients (8%) with LCI versus 36 patients (4.8%) with WLI. This translated to a 1.67-times higher rate of detection.

First-pass WLI missed 26 lesions that were picked up by second-pass LCI. Five lesions were missed by LCI and were subsequently detected by WLI, which translated to a greater than 80% reduction in missed lesions with LCI.

Procedure time was longer with LCI than WLI, but mean differences were less than 20 seconds.

The investigators said that there is a possibility of overdiagnosis with both systems, but perhaps more so with LCI. Overall, WLI detected 121 lesions on first pass, 30.6% of which were neoplastic; first-pass LCI detected 185 lesions, 35.7% of which were neoplastic.

The trial was funded by Fujifilm. One investigator has received a grant and another has received research funding from Fujifilm. Dr. Ryou is a consultant for the company.

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77), the cure rate of triple-therapy regimens increased by 6%-10% with high doses of PPIs. However, Dr. Nyssen and colleagues found that 48% of triple therapies included low doses of PPIs. This number decreased over time, the authors noted: from 67% in 2013 to 20% in 2019. "From another perspective, the daily PPI dose has increased from a dose equivalent to 54 mg of omeprazole in 2013 to 104 mg in 2019," they wrote.

The other four errors they discussed were failing to adequately consider penicillin allergies in prescription choices, failing to consider the importance of treatment compliance, repeating certain antibiotics after failures, and not checking eradication success after treatment.

Based on these findings, Dr. Nyssen and colleagues suggested that "penetration of recommendations in the participating European countries is still poor and delayed, even though some improvements from guidelines have been partially incorporated."

According to Grigorios I. Leontiadis, MD, PhD, of McMaster University, Hamilton, Ont., who coauthored the 2017 American College of Gastroenterology *H. pylori* management guidelines and the Canadian Association of Gastroenterology "Toronto Consensus" in 2016, "This study is important and timely given the steadily increasing antibiotic resistance of *H. pylori* worldwide."

Although Dr. Leontiadias described the results as "suboptimal," he was partially reassured by the improvements over time, "especially following publication of the 2016 European clinical practice guidelines." He also noted that some older clinical practice guidelines issued conditional recommendations, which could "justify the lower adherence seen in the early period of this study."

"The unanswered question," Dr. Leontiadias went on, "is whether the practice of gastroenterologists who volunteered to participate in this prospective registry is truly representative of how *H. pylori* is managed in Europe. Most likely it isn't. Nonparticipating gastroenterologists and nongastroenterologist health care practitioners are probably less aware of and less adherent to clinical practice guidelines. This means that the actual situation in the real world is probably grimmer than what this study shows."

William D. Chey, MD, AGAF, Nostrant Collegiate Professor of Gastroenterology at the University of Michigan, Ann Arbor, considered the results "not entirely surprising, but nonetheless, noteworthy."

Dr. Chey noted that the United States lacks a similar registry to compare real-world *H. pylori* management; even so, he suggested several findings that "bear reiteration" for clinicians in the United States.

"Since U.S. providers do not have reliable data on *H. pylori* antimicrobial resistance, it is useful to ask about prior macrolide antibiotic exposure, and if a patient has received a macrolide for any reason, clarithromycin triple therapy should be avoided. Bismuth quadruple therapy remains a reliable first-line treatment option in the U.S. Another recently approved first-line treatment option is the combination of a proton pump inhibitor, rifabutin, and amoxicillin. Treatment regimens in the U.S. should be given for a minimum of 10 days and, preferably, for 14 days. Another point made by the article is that providers should be maximizing gastric acid suppression by using higher doses of proton pump inhibitors when treating *H. pylori*."

Dr. Chey also noted an emerging treatment option that could soon be available. "Results from phase 3 trials in North America and Europe with the potassium-competitive acid blocker vonoprazan combined with amoxicillin, with and without clarithromycin, are expected in 2021 and may provide another novel first-line treatment option."

Dr. Nyssen and colleagues disclosed relationships with Allergan, Mayoly, Janssen, and others. Dr. Leontiadias disclosed no conflicts of interest. Dr. Chey is a consultant for Redhill, Phathom, and Takeda, which is developing vonoprazan.

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Nonmetabolic factors also at play

NAFLD *from page 1*

higher costs, but not higher rates of death among patients with both Crohn's disease or ulcerative colitis and NAFLD. The researchers analyzed data from patients in the Nationwide Readmissions Database (2016-2017), using ICD-10 codes to identify patients with IBD and NAFLD, along with propensity-matched controls. The study included 3,655 with Crohn's disease and NAFLD and 7,482 without, and there were 2,026 with ulcerative colitis and NAFLD 4,094 without.

IBD hospital readmission rates were higher with comorbid NAFLD in Crohn's disease (hazard ratio, 1.98; 95% confidence interval, 1.8-2.17; $P < .001$) and ulcerative colitis (HR, 1.97; 95% CI, 1.67-2.32; $P < .001$). Comorbid NAFLD was associated with additional length of stay Crohn's disease (0.74 days; 95% CI, 0.29-1.18; $P < .01$) and ulcerative colitis (0.84 days; 0.32-1.35, respectively; $P < .01$), and there was additional cost of care with both Crohn's disease ($7,766; 95% CI, $2,693-$12,839; $P < .01$) and ulcerative colitis ($11,496; 95% CI, $4,361-$18,631; $P < .01$).

Although evidence points to metabolic factors such as obesity and diabetes being involved, nonmetabolic factors are likely important as well. "We still do recognize that it's very likely that these metabolic factors play a role in developing NAFLD in IBD. I think the fact that there are worse outcomes in patients with NAFLD supports the fact that we should do our best to control the metabolic factors like diabetes, obesity, etc. We don't want to minimize that aspect of it. But I think the fact that there were still worse outcomes after adjusting for metabolic factors emphasizes the importance of researching these factors further to see which ones are the main contributors. If we can find the main contributor, whether that's medication, IBD disease burden, or history of surgery, perhaps we can use that information to prevent development or progression of NAFLD," said Dr. Noorian.

"Historical reports have examined the relationship between Crohn's disease and NAFLD. The current study included both Crohn's and ulcerative colitis, thus impressively demonstrating the importance of this interaction across IBD," said Matthew Ciorba, MD, AGAF, director of the IBD Center at Washington University in St. Louis, who attended the session.

Dr. Ciorba

"This is the largest study to date, and the signal is very clear. It really does underscore the need [to study not just how] medications and other factors influence the clinical syndrome, but how it happens mechanistically. There are a multitude of metabolic interactions going on between the gut and liver. We need to understand this better – not just at the systemic level, but at the enterohepatic circulation level," said Dr. Ciorba.

The study also brings to light a potentially emerging problem. "In the past, Crohn's patients were oftentimes thin because their Crohn's disease wasn't well treated. They were taking steroids all the time, so they had fat redistribution, including to the liver. Now we see IBD patients who are obese, and most are not underweight. It has become a compounding problem at this point with both conditions contributing to morbidity," said Dr. Ciorba.

The study had no source of funding. Dr. Noorian and Dr. Ciorba have no relevant financial disclosures.

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AGA Clinical Practice Update

Diagnosis and management of immune checkpoint inhibitor–related enterocolitis and hepatitis

BY AMY KARON
MDedge News

Endoscopy with biopsies is best for diagnosing immune-mediated enterocolitis in patients receiving immune checkpoint inhibitors (ICIs), but another option is to first test the stool for lactoferrin or calprotectin to identify patients with mild diarrhea who could benefit from endoscopy, according to a clinical practice update from the American Gastroenterological Association.

Writing in Gastroenterology (2020 Oct 17. doi: 10.1053/j.gastro.2020.08.063), Michael Dougan, MD, PhD, of Harvard Medical School, Boston, and colleagues noted that stool lactoferrin had been found in one study to be 90% sensitive for detecting histologic inflammation (J Immunother Cancer. 2018 Dec 5;6[1]:142), while another study found that mucosal inflammation is absent in 20%-30% of patients with suspected ICI enterocolitis (J Immunother Cancer. 2019 Nov 7;7[1]:292). Nonetheless, clinicians should consider diagnostic endoscopy before starting high-dose corticosteroids for ICI enterocolitis, especially because "colonic ulceration identified by endoscopy is the only established factor that predicts how ICI enterocolitis will respond to treatment," Dr. Dougan and colleagues wrote. If performed, endoscopy must be prompt because ICI colitis can progress within days, especially if patients are receiving ipilimumab.

ICIs can induce autoimmune inflammation in almost any organ system because they target pathways that regulate autoimmunity, the experts wrote. The gastrointestinal tract is one of the most common sites of toxicity: One study from 2006 (J Clin Oncol. 2006 May 20;24[15]:2283-9) and another from 2019 (Trends Immunol. 2019 Jun;40[6]:511-23) suggested that colitis, with or without enteritis, affects up to 40% of patients depending on the pathway targeted. Oncologists manage most gastrointestinal ICI toxicities, but gastroenterologists and hepatologists often help with complex, atypical, or treatment-refractory cases; to help guide this process, the experts reviewed the literature and made 15 relevant recommendations.

The authors noted that the differential diagnosis is broad, but suggested that *Clostridioides difficile* testing and stool culture or stool pathogen testing should be performed in all patients to rule out infectious causes prior to any immunosuppressive treatments, such as corticosteroids. Imaging is not recommended if a patient has only diarrhea but can help rule out complications if fever, bleeding, or abdominal pain are also present. Laboratory blood tests are rarely informative.

High-dose glucocorticoids are usually effective, often being started at 0.5-2.0 mg/kg prednisone or equivalent daily and tapered over 4-6 weeks after clinical improvement, but these doses and schedules have not been rigorously examined. For glucocorticoid-refractory ICI enterocolitis, infliximab and vedolizumab "are reasonable options" for second-line immunosuppression and should be individualized based on the underlying cancer and other risk factors; patients usually respond to these immunomodulators in less than a week. Most cases of ICI enterocolitis do not recur unless the ICI is restarted, but "many patients require the full loading dose for infliximab or vedolizumab, and maintenance therapy may still be required for certain cases."

ICI-induced hepatitis is less common, affecting less than 5% of patients in clinical trials according to the authors, but incidence rises if patients are on ICI combinations or an ICI plus chemotherapy. Before any ICI is started, patients' total bilirubin, alkaline phosphatase, AST, and ALT levels should be checked, as should presence of hepatitis B. Liver chemistries should be repeated before each ICI cycle, and rising chemistries should trigger an assessment for other causes of liver injury.

Patients with Common Terminology Criteria for Adverse Events (CTCAE) grade 1 hepatitis – defined as AST or ALT 1-3 times the upper limit of normal or total bilirubin 1-1.5 times ULN – should receive liver function tests once or twice weekly. For CTCAE grade 2 hepatitis (AST/ALT more than 3-5 times ULN or total bilirubin more than 1.5-3 times ULN), ICI should be held until resolution to grade 1, and corticosteroids (prednisone or its equivalent dosed at 0.5-1.0 mg/kg daily) should be considered if there are clinical symptoms of liver toxicity. For grade 3 hepatitis (AST/ALT greater than 5-20 times ULN or total bilirubin more than 3-10 times ULN), ICI therapy should be halted, "and urgent consultation with a gastroenterologist/hepatologist is appropriate." In this context, methylprednisone (1-2 mg/kg) is suggested, and azathioprine or mycophenolate mofetil can be considered if clinical hepatitis does not improve in 3-5 days. For CTCAE grade 4 hepatitis, hospitalization is recommended, and patients should permanently stop the ICI and receive 2 mg/kg per day of methylprednisolone or its equivalent.

The authors received no funding support. Dr. Dougan reported consulting or advisory relationships with Neoleukin Therapeutics, Genentech, Tillotts Pharma, and Partner Therapeutics and grant support from Novartis and Genentech. Two coauthors also reported ties to several pharmaceutical companies.

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Racial, social inequities persist in many aspects of IBD

BY JIM KLING
MDedge News

FROM THE CROHN'S & COLITIS CONGRESS

Although inflammatory bowel disease (IBD) affects primarily White patients, about one-quarter of cases are found in non-White racial and ethnic groups. Various factors have combined to lead to disparities in treatment and outcomes for non-Whites with IBD.

Ethnic and racial disparities, along with socioeconomic factors, were the subject of a presentation by Ruby Greywoode, MD, at the annual congress of the Crohn's & Colitis Foundation and the American Gastroenterological Association.

"Historical and present-day realities of racial inequity and factors that contribute to socioeconomic status [include] educational and housing policies, employment practices, and generational wealth. Addressing health disparities requires acknowledging these systemic factors," said Dr. Greywoode, who is with Montefiore Medical Center in New York.

An important concept in discussing health disparity is social determinants of health, which refer to nonbiological factors that affect health and health outcomes. These are "the conditions in which people live, work, learn, and play that affect their health and their quality of life," said Dr. Greywoode.

Dr. Greywoode shared examples of social determinants that affect economic stability and financial worry. One study found that one in six IBD patients reported not taking their medications because of cost considerations (Clin Gastroenterol Hepatol. 2020 Jun 9. doi: 10.1016/j.cgh.2020.05.056). A survey of about 900 adults showed that one in four delayed medical care – half of those because of cost (Inflamm Bowel Dis. 2017 Feb;23[2]:224-32); patients who delayed care were 2.5 times

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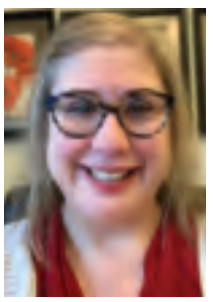
AGA Resource
AGA applauds researchers who are working to raise our awareness of health disparities in digestive diseases. AGA is committed to addressing this important societal issue head on. Learn more about AGA's commitment through the AGA Equity Project. https://gastro.org/aga-leadership/initiatives-and-programs/aga-equity-project/

Holistic approach to IBD advocated

Wellness *from page 1*

pursue happiness, and contribute to the community. "Wellness is defined as a state of complete physical, mental, and social well-being. It's a holistic definition, not merely the absence of those things," she said during her talk.



Dr. Keefer

Social determinants of health, such as income, inequality, health literacy, numeracy, financial stress, social connections, community, place of residence, and housing coresidents play important roles.

"Subjective well-being is a state in which an individual feels they are able to do work productively and creatively, have relationships, and contribute to their community. We want them to thrive. We want them to live well. We want them to reach their potential. There's no reason you cannot reach your potential even though you're living with IBD," said Dr. Keefer.

Subjective well-being doesn't replace quality of life assessment. "Absolutely, quality of life is an important metric, [but I want to] make a plug that maybe we should start to add subjective well-being into these outcome measures," said Dr. Keefer.

The approach does away with specific measures of health, employment, financial security, or even living situation. "It takes away all of those things we just assume are part of being well. It measures it differently. It measures what makes us happy, divided by the degree of happiness we obtain," said Dr. Keefer. She presented examples from a study her group is conducting that showed patients' responses to what made them want to be well. "Some people want to be well to take care of their children or families or a parent, some people want to be well so they can go adventure skydiving, other people just want to be able to exercise and take care of their health. That's what the target needs to be for wellness. In that sense, wellness is an achievement of best health possible in all domains, not just one. It's a lifelong pursuit. It forces us to ask not just 'Are my patient's symptoms gone? Are they in clinical remission? Are they in histological remission? Are they in deep remission?' but 'Is my patient thriving? Are they meeting their potential? Are they getting what they want out of treatment? Are they happy?' "

Ms. Aswani Omprakash

Quality of life measures can provide some insight, but they are limited because they are anchored in physical symptoms, and they focus on a narrow, recent window, usually the past week. "You can imagine that, as symptoms improve, those metrics kind of improve, and it looks like quality of life is great. But that's not always the case, and we're really missing an opportunity to go deeper. It's also less sensitive when somebody is in remission, so it's also very difficult to continue that proactive [approach] of thriving and living well when you're already coming up positive on quality of life indices," said Dr. Keefer.

Subjective well-being measures ignore physical symptoms, and focus instead on questions like the patient's ability to work, socialize, and maintain relationships with family, and whether the patient feels able to contribute meaningfully to society. The measure is insensitive to factors such as inflammation, trauma, or changes to medication. As a result, measures can be used much less frequently – every 6 months, or even once a year.

Subjective well-being can also rely on the patient to define well-being, and that makes it more culturally sensitive. "It can allow for people to be well in whatever way they think they want to be well," said Dr. Keefer.

There are various resources for measuring subjective well-being. The Organization for Economic Cooperation and Development has guidelines for measuring subjective well-being. The National Institutes of Health PROMIS includes useful measures of psychological well-being, positive affect, and general life satisfaction; they are available for free and include six to eight items. Other useful measures include the Satisfaction With Life scale, the Positive and Negative Affect scale, and the Harmony in Life scale. "All of those have been well validated and used internationally as measures of well-being," said Dr. Keefer.

Physicians can also address patients directly, asking them about how satisfied they are with their life. "You're opening up that discussion to ask them not just, 'How is your IBD and how is your IBD affecting your work?' but 'How is your life going?' You're proactively trying to help your patients thrive," said Dr. Keefer.

Session moderators praised Dr. Keefer's presentation as an appropriate wrap-up to talks that looked at stress, diet, economic disparities, health literacy, and numeracy.

"We capped it all with a discussion around what is well-being. We often talk about biologics or medicines or surgery when it comes to Crohn's disease and ulcerative colitis, but what about holistic wellness? It's all of this. It's the medication piece, but it's all of these other pillars involved in the process as well. I think looking at this from many different angles is very important so that patients can achieve the best quality of life possible," said comoderator Tina Aswani Omprakash, a patient advocate who is pursuing a master's degree in public health at Mount Sinai's Icahn School of Medicine.

Ms. Issokson

The other comoderator, Kelly Issokson, agreed. "You can't adequately treat patients with diet alone or stress management alone. You really need a holistic approach for best outcomes," said Ms. Issokson of the digestive disease clinic at Cedars-Sinai Medical Center in Los Angeles.

Dr. Keefer has received research funding from AbbVie and is a cofounder and equity holder in Trellus Health. Ms. Aswani Omprakash has consulted for Genentech, AbbVie, Janssen, and Arena Pharmaceuticals. Ms. Issokson has no relevant financial disclosures.

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Continued from previous page

more likely to report an IBD flare in the previous year.

Another important issue is food insecurity. Session comoderator Kelly Issokson noted that socioeconomic factors often interfere with adoption of healthy diets. Whole foods and plant-based foods are expensive, and the financial pressures of the COVID-19 epidemic have made that worse. "Millions of people are slipping into poverty and food insecurity," said Ms. Issokson, who is with the digestive disease clinic at Cedars-Sinai Medical Center in Los Angeles.

Dr. Greywoode also described studies that looked at IBD outcomes. A review from 2013 showed disparities among Whites, African Americans, and Hispanics with respect to undergoing ulcerative colitis–related colectomy and Crohn's disease–related bowel resection (Inflamm Bowel Dis. 2013 Mar;19[3]:627-43). Ulcerative colitis patients on Medicaid had 230% greater in-patient mortality, compared with patients with private insurance, even after adjustment for multiple confounders.

But inequities are not static. "Since this publication, we have numerous other studies drawing conclusions that sometimes agree with and sometimes conflict with it. My belief is that health disparities in IBD will continue to be an active area of research. We know that it takes vigilance to identify, track, and address any disparities when they do arise," said Dr. Greywoode.

"As we move forward in IBD research, we recognize that individuals of European ancestry are not the only ones who have IBD. There is a growing diverse racial and ethnic population with IBD," said Dr. Greywoode. She noted that, in the United States, it is estimated that about one in four adult patients are not White (MMWR Morb Mortal Wkly Rep. 2016;65:1166-9). Nevertheless, Whites are overrepresented in IBD clinical trials, with some including up to 95% White patients or not listing race at all. "[W]e know that what is not collected is not measured, and what is not measured can't be evaluated, either to praise or constructively criticize," said Dr. Greywoode.

Fortunately, there are efforts in place to improve representation in clinical trials. There has been a mandate for almost 3 decades that federally funded research must include racial and ethnic minorities who have been traditionally underrepresented. The Food and Drug Administration has also provided guidance to industry to improve diversity in clinical trial participation, and industry groups have developed strategies, including improved representation among investigators and related early–career development programs. Clinical trial networks encourage patient participation with regulatory and data management support to bolster practices with insufficient resources.

Dr. Greywoode and Ms. Issokson have no relevant financial disclosures.

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IBD in pandemic reinforces need to taper steroids

BY JIM KLING
MDedge News

FROM THE CROHN'S & COLITIS CONGRESS

Multicenter and population cohort studies suggest that patients with inflammatory bowel disease (IBD) are not at unique risk of contracting COVID-19 or experiencing worse outcomes, with the exception of a few risk factors such as corticosteroid use and combination therapy that appear tied to greater risk of hospitalization and mortality. The findings line up well with previous experience with infectious disease and are reassuring, but they also underscore the need to taper steroids and de-escalate from combination therapy, when possible.

"There is not a clear increased risk of getting COVID-19 among IBD patients compared to the general population, and that seems to hold even if you look at certain medication types, [even] if patients are on immunosuppressives like thiopurines or anti-TNF [anti–tumor necrosis factor] drugs," Ryan C. Ungaro, MD, said in an interview. Dr. Ungaro, who is with Icahn School of Medicine at Mount Sinai, New York, discussed IBD and COVID-19 risks at the annual congress of the Crohn's & Colitis Foundation and the American Gastroenterological Association.

A systematic review showed that 0.3% of IBD patients contracted COVID-19 during study periods, compared with 0.2%-4.0% of the general population (Inflamm Bowel Dis. 2020 Sep 18;26[10]:e132-3), and a matched-cohort analysis of a national Veterans Affairs database showed an infection prevalence of 0.23% among patients with IBD versus 0.20% among those without (P = .29) (Am J Gastroenterol. 2020 Oct 19. doi: 10.14309/ajg.0000000000001012).

Studies show that patients with IBD in general do not appear to be at greater risk of severe disease outcomes such as hospitalization or 30-day mortality. For example, a U.S. national database study of more than 40 million patients compared 232 patients with IBD who were diagnosed with COVID-19 with 19,776 non-IBD patients and found that, after propensity matching, there were no significant association between IBD and worse outcomes (risk ratio, 0.93; 95% confidence interval, 0.68-1.27; P = .86) or hospitalizations (RR, 1.10; 95% CI, 0.74-1.40; P = .91) (Gastroenterology. 2020 Oct;159[4]:1575-8.e4).

However, some risk factors could be red flags. Data from the international SECURE-IBD registry (Gastroenterology. 2020 Aug;159[2]:481-91.e3) associated severe COVID-19 with use of corticosteroids (adjusted odds ratio, 6.87; 95% CI, 2.30-20.51; P < .001). In terms of other therapies, another study found a similar effect with thiopurines (compared with TNF monotherapy; aOR, 4.08; 95% CI, 1.65-9.78; Bonferroni adjusted P = .008), and combined use of anti-TNF drugs and a thiopurine (compared with TNF monotherapy; aOR, 4.01; 95% CI, 1.73-9.61; Bonferroni adjusted P = .013), but anti-TNF therapies alone trended toward a protective effect (compared with no anti-TNF therapy; aOR, 0.69; Bonferroni adjusted P = .52) (Gut. 2020. doi: 10.1136/gutjnl-2020-322539). That study found no significant association between severe outcomes and anti-IL 12/23 (compared with anti-TNF monotherapy; aOR, 0.98; 95% CI, 0.12-8.06; P = .98) or anti-integrin biologics (compared with anti-TNF monotherapy; aOR, 2.42; 95% CI, 0.59-9.96; P = .22).


Dr. Ungaro

Overall, the data are "generally consistent with prior data on infections and IBD: that steroids and combination therapy increase the risk of infection and bad outcomes and that interestingly biologic monotherapy may actually confer a little bit of protection against emergent outcomes and at a minimum appears to be neutral," said Dr. Ungaro.

"I think the recent data is reassuring that potentially in asymptomatic and maybe even mild cases, the monotherapy biologics – we can consider not delaying administering those," Dr. Ungaro said during the presentation.

"[Tapering patients off corticosteroids or combination therapies is] something we were doing in regular IBD care beforehand, but the COVID-19 pandemic offers another reason to limit the use of steroids and evaluate if patients are able to de-escalate from combination therapies," said Dr. Ungaro.

There was concern among some patients early in the pandemic that their immunotherapy drugs may put them at risk of contracting COVID-19, which led some to discontinue medications, according to David T. Rubin, MD, professor of medicine at the University of Chicago and chair of the congress's organizing committee. "The data do not in general suggest you should do that to protect yourself. In fact, being on the therapies may have a better outcome. ... Getting sick from your Crohn's disease or colitis, when there are limited health care resources and, in some places, limited hospital beds and where the rescue therapy might include steroids, is a risky proposition. It's not the time to do this," said Dr. Rubin.

With respect to vaccines, it appears so far that there is no increased risk of adverse events associated with IBD. Patients who are on immunosuppressive drugs may experience a lower response to immunization, which has been seen with other vaccines.

Dr. Ungaro is on the advisory board for Bristol-Myers Squibb, Janssen, Pfizer, and Takeda. He has received funding from AbbVie, Boehringer Ingelheim, Eli Lilly, and Pfizer. He has been a speaker or received consulting fees from AbbVie and Eli Lilly. Dr. Rubin is a consultant for Janssen, Pfizer, Takeda, and AbbVie.

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AGA Resource
For the latest clinical guidance, education, research, and physician resources about coronavirus, visit the AGA COVID-19 Resource Center at www.gastro.org/COVID.

Younger adults present with more advanced esophageal adenocarcinoma

BY HEIDI SPLETE
MDedge News

The incidence of esophageal adenocarcinoma in adults aged younger than 50 years increased threefold between 1975 and 2015, based on data from more than 34,000 cases.

Esophageal carcinoma rates overall have risen in the United States over the past 4 decades, but the average patient is in their 60s, wrote Don C. Codipilly, MD, of the Mayo Clinic, Rochester, Minn., and colleagues. Therefore, "data on the incidence, stage distribution, and outcomes of this segment of patients [younger than 50 years] with esophageal adenocarcinoma are relatively limited."

In a study published in Cancer Epidemiology, Biomarkers & Prevention (2020 Dec 11. doi: 10.1158/1055-9965.EPI-20-0944), the researchers identified 34,443 cases of esophageal adenocarcinoma using the Surveillance, Epidemiology, and End Results (SEER) database for the periods of 1975-1989, 1990-1999, and 2000-2015. The cases were limited to histologically confirmed cases and were stratified according to age at diagnosis: younger than 50 years, 50-69 years, and 70 years and older.

Overall, the annual incidence of esophageal adenocarcinoma among individuals younger than 50 years increased from 0.08 per 100,000 persons in 1975 to 0.27 per 100,000 persons in 2015.

Although the incidence rose across all three age groups during the study period, the largest increase was seen in those aged 70 years and older. However, the younger group was significantly more likely to present at more-advanced stages, the researchers pointed out: Between 2000 and 2015, localized disease represented only 15.1% of cases in those younger than 50 years, compared with 22.4% in patients aged 50-69 years and 32.2% in those 70 years and older. The incidence of regional/distant disease among younger patients has increased over time, with 81.8% in 1975-1989, 75.5% in 1990-1999, and 84.9% in 2000-2015 ($P < .01$), and this increase has been faster than among older groups, the researches noted. For comparison, during 2000-2015 only 77.6% of patients aged 50-69 years and 67.8% of patients 70 years and older had regional/distant disease.

In addition, the majority of cases of young-onset esophageal adenocarcinoma occurred in men in a trend that persisted across the study periods; 90% of patients younger than 50 years were male in 1975, and 86% of the younger patients in 2015 were male.

"There is no clear explanation for the higher proportion of advanced disease in younger patients, and further study is required to identify biologic, genetic, and environmental factors that may underlie this observation," the researchers wrote. "A potential hypothesis is that 'young-onset esophageal adenocarcinoma' may involve rapid transition from intestinal metaplasia to esophageal adenocarcinoma, driven by an increase in signaling molecules that are active in the intestine."

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Endoscopic CRC resection carries recurrence, mortality risks

BY WILL PASS
MDedge News

After endoscopic resection, high-risk T1 colorectal cancer (CRC) may have a 10-fold greater risk of recurrence than low-risk disease, based on a meta-analysis involving more than 5,000 patients.

These findings support personalized, histologically based surveillance strategies following endoscopic resection of T1 CRC, reported lead author Hao Dang of Leiden (the Netherlands) University Medical Center and colleagues.

"With the introduction of population-based screening programs, a growing number of early-invasive colorectal cancers (T1 CRCs) are detected and treated with local endoscopic resection," the investigators wrote in Clinical Gastroenterology and Hepatology (2020 Nov 30. doi: 10.1016/j.cgh.2020.11.032). Success with this approach, however, depends upon accurate risk recurrence data, which have been lacking.

Joseph Feuerstein, MD, of the department of medicine at Harvard Medical School and associate clinical chief of gastroenterology at Beth Israel Deaconess Medical Center, Boston, said, "While attempting complete resection of an early cancer with a colonoscopy is appealing, given the very low morbidity associated with it, this technique is only advisable if the risk of recurrence is extremely low when comparing [it] to surgical resection."

Accurate recurrence data could also inform postoperative surveillance: "To determine the optimal frequency and method of surveillance, it is important to know how often, and at which moments in follow-up local or distant CRC recurrences exactly occur," wrote Mr. Dang and colleagues. "However, for endoscopically treated T1 CRC patients, the definite answers to these questions have not yet been provided."

To find answers, Mr. Dang and colleagues conducted a meta-analysis involving 71 studies and 5,167 patients with endoscopically treated T1 CRC. The primary outcome was cumulative incidence and time pattern of CRC recurrence. Data were further characterized by local and/or distant metastasis and CRC-specific mortality.

The pooled cumulative incidence of CRC recurrence was 3.3%, with local and distant recurrences occurring at similar, respective rates of 1.9% and 1.6%. Most recurrences (95.6%) occurred within 72 months of endoscopic resection. Risk-based recurrence analysis revealed a distinct pattern, with high-risk T1 CRCs recurring at a rate of 7.0% (95% confidence interval, 4.9%-9.9%), compared with just 0.7% for low-risk tumors (95%-CI, 0.4%-1.2%). Mortality data emphasized the clinical importance of this disparity as the CRC-related mortality rate was 1.7% across the population versus 40.8% among patients with recurrence.

"Our meta-analysis provides quantitative measures of relevant follow-up outcomes, which can form the basis for evidence-based surveillance recommendations for endoscopically treated T1 CRC patients," the investigators concluded.

According to Dr. Feuerstein, the findings highlight the importance of surveillance after endoscopic resection of CRC while adding clarity to appropriate timing.

"Current guidelines recommend a colonoscopy following a colon cancer diagnosis at 1 year and then 3 years and then every 5 years," Dr. Feuerstein said. "Adhering to these guidelines would likely identify most cases of recurrence early on within the 72-month window identified in this study." He noted that "high-risk T1 CRC should probably be monitored more aggressively."

Anoop Prabhu, MD, of the department of medicine at the University of Michigan Medical Center and director of endoscopy at Ann Arbor Veterans Affairs Medical Center, drew similar conclusions from the findings, noting that "tumor histology appears to be a powerful risk-stratification tool for subsequent surveillance."

"One of the most important take-home messages from this paper is that, in those patients with low-risk, endoscopically resected colon cancer, surveillance with a colonoscopy in 1 year (as opposed to more intense endoscopic or radiographic surveillance) is likely more than adequate and can save unnecessary testing," Dr. Prabhu said.

To build on these findings, Dr. Prabhu suggested that upcoming studies could directly compare different management pathways.

The investigators disclosed relationships with Boston Scientific, Cook Medical, and Medtronics. Dr. Feuerstein and Dr. Prabhu reported no relevant conflicts of interest.

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AGA Resource
Help your patients understand colorectal cancer prevention and screening options by sharing AGA's patient education from the GI Patient Center: www.gastro.org/CRC.

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The study findings were limited by several factors including the inability to review individual case records to confirm disease stage and to compare outcomes across ethnicities, and the lack of data on comorbidities in the SEER database, the researchers noted.

However, the results were strengthened by overall quality of the SEER database and use of multivariate analysis, they added. The evidence of increased incidence and increased odds of advanced disease in younger adults suggest that "reevaluation of our diagnostic and treatment strategies in this age group might need to be considered."

Reasons for increase remain unclear

"While esophageal adenocarcinoma is uncommon overall in younger patients, this study importantly highlights that not only has the incidence of esophageal adenocarcinoma increased more than threefold in patients under the age of 50 over the last 4 decades, but that younger patients are presenting with more advanced disease and have overall poorer survival, compared to older patients," Rahul A. Shimpi, MD, of Duke University, Durham, N.C., said in an interview.

"The reasons for these findings are unclear, but the authors propose a number of potential factors that could explain them. These include differences in tumor biology, rising rates of obesity and [gastroesophageal reflux disease] in younger patients, decreased endoscopic screening for and surveillance of Barrett's esophagus in this age group, and differing therapeutic approaches to management," Dr. Shimpi said.

"The findings from this study underscore that, while uncommon, clinicians need to be aware of the rising incidence of esophageal cancer in younger patients. It is important that even younger patients presenting with esophageal symptoms, such as dysphagia, undergo investigation," he emphasized.

"I would like to see further study into the potential factors driving the findings in this study, including whether trends in differential treatment modalities account for some of the survival differences found in different age groups," Dr. Shimpi added. "Finally, further research will ideally clarify optimal Barrett's screening and surveillance approaches in patients younger than age 50 in order to determine whether new strategies might impact esophageal adenocarcinoma incidence and outcomes in this group."

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