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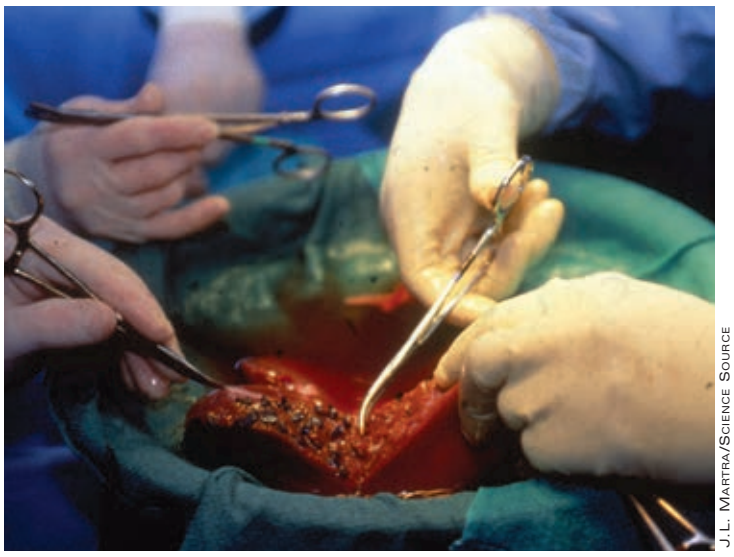

J.L. Martra/Science Source

A new study suggests racial disparities persist in getting listed for transplant. Once patients are on a list, the disparities greatly decrease.

Minorities underrepresented on liver transplant lists

BY WILL PASS

Non-Hispanic Black and Hispanic patients are underrepresented on many liver transplant waiting lists, whereas non-Hispanic White patients are often overrepresented, according to data from 109 centers.

While racial disparities "greatly diminished" after placement on a waiting list, which suggests recent progress in the field, pre–wait-listing disparities may be more challenging to overcome, reported lead author Curtis Warren, MPH, CPH, of the University of Florida, Gainesville, and colleagues.

"In 2020, the Organ Procurement and Transplantation Network implemented a new allocation system for liver transplantation based on concentric circles of geographic proximity rather than somewhat arbitrarily delineated Donor Service Areas (DSAs)," the investigators wrote in Journal of the American College of Surgeons (2021 Jan 11. doi: 10.1016/j.jamcollsurg.2020.12.021). "Although this was a step

See **Minorities** · *page 30*

Infliximab weakens COVID-19 antibody response among patients with IBD

BY HEIDI SPLETE

Patients treated with infliximab for inflammatory bowel disease (IBD) showed significantly reduced response to COVID-19 antibodies, compared with those treated with vedolizumab, according to data from nearly 7,000 patients.

Although anti–tumor necrosis factor (anti-TNF) drugs are routinely used for patients with IBD, the impact of their immune-suppressing properties on protective immunity to COVID-19 is unknown, wrote Nicholas A. Kennedy, MD, of the University of Exeter (England) and colleagues. These drugs have been reported to impair protective immunity following vaccines for other diseases, such as those for influenza (Inflamm Bowel Dis. 2019 Mar 4;26[4]:593-602) and viral hepatitis (Inflamm Bowel Dis. 2018 Jan 18;24[2]:380-6).

"By suppressing immune responses, biological and immunosuppression therapies may lead to chronic SARS-CoV-2 infection and have recently been implicated in the evolution and emergence of novel variants," they

See **Infliximab** · *page 36*

INSIDE

AGA Clinical Practice Guidelines

How intragastric balloons can be used to manage obesity

BY AMY KARON

For patients with obesity who want to lose weight but for whom conventional weight-loss strategies have failed, the combination of intragastric balloon placement and lifestyle modifications may be preferable to lifestyle modifications alone, according to new clinical practice guidelines from the American Gastroenterological Association.

In randomized clinical trials of patients with

See **Balloons** · *page 19*

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LETTER FROM THE EDITOR

Spring into tomorrow on the right foot

This May, DDW will again be a virtual meeting. Not only does this pandemic continue, but it has re-emerged with a vengeance in several states. Michigan leads the nation in cases per 100,000, with the U.K. variant now predominant. Younger adults are being most impacted. There have been almost 250 confirmed COVID-19 cases in fully vaccinated people in Michigan (Weixel N. Michigan officials found only 246 COVID-19 cases among fully vaccinated. The Hill. 2021 Apr 7. Accessed 2021 Apr 13). COVID-19 will be with us for a long time.


Dr. Allen

Despite the disruption caused by the coronavirus, scientific research and the need for up-to-date education continues. There are numerous educational sessions that will be available for us to view and opportunities for interacting with speakers in many. I hope you will take advantage of a virtual DDW to refresh knowledge and learn about new modalities to care for our patients.

I hope you continue to take care of yourself, your families, and those in your communities.

Three cover stories this month should be of interest. A new AGA guideline has been published, and it recognizes the advances made in construction and use of intragastric balloons. Current balloons positively add to weigh loss and, when used correctly, are safer and more effective than in the past. Gastroenterologists should enter the bariatric arena in multiple ways from lifestyle counseling to endoscopic therapies. We have much to add to this field. Another cover article concerns infliximab's influence on development of COVID-19 antibodies. The last discusses how minority status influences liver transplant listing; we continue to uncover the impact of implicit bias in our medical decisions.

I hope you continue to take care of yourself, your families, and those in your communities. We are close to a return to normalcy but are not out of the woods yet. This is a time of reset in our nation, and we all should remember that we are a social network that works only when we look beyond ourselves. I have quoted Tom Friedman before: "Respect science, respect nature, respect each other."

Have a happy and healthy spring.

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


Wolfgang Filser/EyeEm/Getty Images

Top cases

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. Here's a preview of a recent popular clinical discussion:

From Jennifer Weiss, MD, MS, AGAF: Implementing CRC screening at 45:

The ACS recommended lowering the CRC screening age to 45, ACG has recently followed suit, and the USPSTF draft revisions also support a lower CRC screening age.

In this month of colorectal cancer awareness, I was wondering how many people have started implementing this change in their practice and if they have received any pushback from insurance companies?

See how AGA members responded and join the discussion: https://community.gastro.org/posts/23923.

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Surveillance may perform better than expected

BY WILL PASS

For patients with Barrett's esophagus, surveillance endoscopy detects high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC) more often than previously reported, according to a retrospective analysis of more than 1,000 patients.

Neoplasia detection rate, defined as findings on initial surveillance endoscopy, was also lower than that observed in past studies, according to lead author Lovekirat Dhaliwal, MBBS, of Mayo Clinic, Rochester, Minn., and colleagues.

This study's findings may help define quality control benchmarks for endoscopic surveillance of Barrett's esophagus, the investigators wrote in Clinical Gastroenterology and Hepatology (2020 Jul. doi: 10.1016/j.cgh.2020. 07.034). Accurate metrics are needed, they noted, because almost 9 out of 10 patients with Barrett's esophagus present with EAC outside of a surveillance program, which "may represent missed opportunities at screening." At the same time, a previous study by the investigators (Gastroenterology. 2016 Mar;150[3]:599-607.e7) and one from another group (United European Gastroenterol J. 2018 May;6[4]:519-28), have suggested that 25%-33% of HGD/EAC cases may go undetected by initial surveillance endoscopy.

Dr. Dhaliwal

Almost 9 out of 10 patients with Barrett's esophagus present with EAC outside of a surveillance program, which "may represent missed opportunities at screening."

"Dysplasia detection in [Barrett's esophagus] is challenging because of its patchy distribution and often subtle appearance," the investigators indicated. "Lack of compliance with recommended biopsy guidelines is also well-documented."

On the other hand, Dr. Dhaliwal and colleagues suggested that previous studies may not accurately portray community practice and,

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therefore, have limited value in determining quality control metrics. A 2019 review (Gut. 2019 Dec;68[12]:2122-8), for instance, reported a neoplasia detection rate of 7% among patients with Barrett's esophagus, but this finding "is composed of data from largely referral center cohorts with endoscopy performed by experienced academic gastroenterologists," they wrote, which may lead to overestimation of such detection.

The authors sought to better characterize this landscape, so they conducted a retrospective analysis that included 1,066 patients with Barrett's esophagus who underwent initial surveillance endoscopy between 1991 and 2019. Approximately three out of four surveillance endoscopies (77%) were performed by gastroenterologists, while the remaining were performed by nongastroenterologists, such as family practitioners or surgeons. About 60% of patients were adequately biopsied according to the Seattle protocol.

Analysis revealed that the neoplasia detection rate was 4.9% (95% confidence interval, 3.8%-6.4%), which is less than the previously reported rate of 7%. HGD was more common than EAC (33 cases vs. 20 cases). Out of 1,066 patients, 391 without neoplasia on initial endoscopy underwent repeat endoscopy within a year. Among these individuals, HGD or EAC was detected in eight patients, which suggests that 13% of diagnoses were missed on initial endoscopy, a rate well below the previously reported range of 25%-33%.

DenGuy/E+/Getty Images

Technology challenged by technique

The neoplasia detection rate "appeared to increase significantly from 1991 to 2019 on univariate analysis (particularly after 2000), but this was not observed on multivariate analysis," the investigators wrote. "This was despite the introduction of high definition monitors and high resolution endoscopes in subsequent years.

"This may suggest that in a low dysplasia prevalence setting, basic techniques such as careful white light inspection of the [Barrett's esophagus] mucosa along with targeted and Seattle protocol biopsies may be more important," they noted.

The importance of technique may be further supported by another finding: Gastroenterologists detected neoplasia almost four times as often as did nongastroenterologists (odds ratio, 3.6; $P = .0154$).

"This finding is novel and may be due to additional training in endoscopy, lesion recognition, and familiarity with surveillance guidelines in gastroenterologists," the investigators wrote. "If this finding is replicated in other cohorts, it may support recommendations for the performance of surveillance by endoscopists trained in gastrointestinal endoscopy and well-versed in surveillance guidelines.

"[U]sing neoplasia detection as a quality metric coupled with outcome measures such as missed dysplasia rates could improve adherence to established biopsy protocols and improve the quality of care to patients," they wrote. "Ultimately, this can be an opportunity to develop a high-value, evidence-based quality metric in [Barrett's esophagus] surveillance."

The authors acknowledged some limitations to their study. Its retrospective design meant no single, uniform biopsy protocol could be adopted across the entire study period; however, the results were "unchanged" when restricted to the period after introduction of the Seattle protocol in 2000. The study's long period could have left results susceptible to changing guidelines; however, when examined, the neoplasia detection rates remained relatively stable over time.

"Because prior reports consisted largely of tertiary care center cohorts, our findings may reflect the absence of referral bias and be more generalizable," the investigators wrote.

The study was funded by the National Institute of Aging and the National Cancer Institute. The investigators disclosed relationships with Celgene, Nine Point Medical, Takeda, and others.

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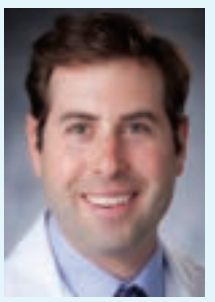
The current study by Dr. Dhaliwal and colleagues evaluates the neoplasia detection rate (NDR) for high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) during surveillance endoscopy, which is a proposed novel quality metric for Barrett's esophagus (BE). Within a population cohort, the investigators found the NDR was 4.9%, and this did not increase significantly during the study period from 1991 to 2019. Gastroenterologists were more likely to report visible abnormalities during endoscopy, and this was a significant predictor of neoplasia detection in a multivariable model. However, the overall rate of missed HGD or EAC was 13%, and this was not associated with procedural specialty. Interestingly, even with only 57% adherence to Seattle protocol in this study, there was no association with missed lesions.



Dr. Leiman

Despite advances in endoscopic imaging and measures establishing quality for biopsy technique, there remains substantial room for improvement in the endoscopic management of patients with BE. While unable to evaluate all factors associated with neoplasia detection, the authors have provided an important real-world benchmark for NDR. Further study is needed to establish the connection between NDR and missed dysplasia, as well as its impact on outcomes such as EAC staging and mortality. Critically, understanding the role of specialized training and other factors such as inspection time to improve NDR is needed.

David A. Leiman, MD, MSHP, is the chair of the AGA Quality Committee. He is an assistant professor of medicine at Duke University, Durham, N.C., where he serves as director of esophageal research and quality. He has no conflicts.

Low-risk adenomas may not elevate risk of CRC-related death

BY WILL PASS

Unlike high-risk adenomas (HRAs), low-risk adenomas (LRAs) have a minimal association with risk of metachronous colorectal cancer and no relationship with odds of metachronous CRC-related mortality, according to a meta-analysis of more than 500,000 individuals.

These findings should impact surveillance guidelines and make follow-up the same for individuals with LRAs or no adenomas, reported lead author Abhiram Duvvuri, MD, of the division of gastroenterology and hepatology at the University of Kansas, Kansas City, and colleagues. Currently, the United States Multi-Society Task Force on Colorectal Cancer advises colonoscopy intervals of 3 years for individuals with HRAs, 7-10 years for those with LRAs, and 10 years for those without adenomas (Gastroenterology. 2020 Mar;158[4]:1131-53.e5).

Dr. Duvvuri

"The evidence supporting these surveillance recommendations for clinically relevant endpoints such as cancer and cancer-related deaths among patients who undergo adenoma removal, particularly LRA, is minimal, because most of the evidence was based on the surrogate risk of metachronous advanced neoplasia," the investigators wrote in Gastroenterology (2021 Jan 29. doi: 10.1053/j.gastro.2021.01.214).

To provide more solid evidence, the investigators performed a systematic review and meta-analysis, ultimately analyzing 12 studies with data from 510,019 individuals at a mean age of 59.2 years. All studies reported rates of LRA, HRA, or no adenoma at baseline colonoscopy, plus incidence of metachronous CRC and/or CRC-related mortality. With these data, the investigators determined incidence of metachronous CRC and CRC-related mortality for each of the adenoma groups and also compared these incidences per 10,000 person-years of follow-up across groups.

After a mean follow-up of 8.5 years, patients with HRAs had a significantly higher rate of CRC compared with patients who had LRAs (13.81 vs. 4.5; odds ratio, 2.35; 95% confidence interval, 1.72-3.20) or no adenomas (13.81 vs. 3.4; OR, 2.92; 95% CI, 2.31-3.69). Similarly, but to a lesser degree, LRAs were associated with significantly greater risk of CRC than that of no adenomas (4.5 vs. 3.4; OR, 1.26; 95% CI, 1.06-1.51).

Data on CRC-related mortality further supported these minimal risk profiles because LRAs did not significantly increase the risk of CRC-related mortality compared with no adenomas (OR, 1.15; 95% CI, 0.76-1.74). In contrast, HRAs were associated with significantly greater risk of CRC-related death than that of both LRAs (OR, 2.48; 95% CI, 1.30-4.75) and no adenomas (OR, 2.69; 95% CI, 1.87-3.87).

The investigators acknowledged certain limitations of their study. For one, there were no randomized controlled trials in the meta-analysis, which can introduce bias. Loss of patients to follow-up is also possible; however, the investigators noted that there was a robust sample of patients available for study outcomes all the same. There is also risk of comparability bias in that HRA and LRA groups underwent more colonoscopies; however, the duration of follow-up and timing of last colonoscopy were similar among groups. Lastly, it's possible the patient sample wasn't representative because of healthy screenee bias, but the investigators compared groups against general population to minimize that bias.

The investigators also highlighted several strengths of their study that make their findings more reliable than those of past meta-analyses. For one, their study is the largest of its kind to date, and involved a significantly higher number of patients with LRA and no adenomas. Also, in contrast with previous studies, CRC and CRC-related mortality were evaluated rather than advanced adenomas, they noted.

"Furthermore, we also analyzed CRC incidence and mortality in the LRA group compared with the general population, with the [standardized incidence ratio] being lower and [standardized mortality ratio] being comparable, confirming that it is indeed a low-risk group," they wrote.

Considering these strengths and the nature of their findings, Dr. Duvvuri and colleagues called for a more conservative approach to CRC surveillance among individuals with LRAs, and more research to investigate extending colonoscopy intervals even further.

"We recommend that the interval for follow-up colonoscopy should be the same in patients with LRAs or no adenomas but that the HRA group should have a more frequent surveillance interval for CRC surveillance compared with these groups," they concluded. "Future studies should evaluate whether surveillance intervals could be lengthened beyond 10 years in the no-adenoma and LRA groups after an initial high-quality index colonoscopy."

One author disclosed affiliations with Erbe, Cdx Labs, Aries, and others. Dr. Duvvuri and the remaining authors disclosed no conflicts.

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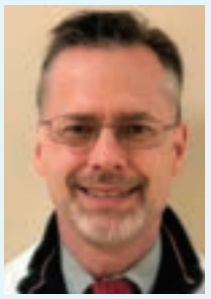
Despite evidence suggesting that colorectal cancer (CRC) incidence and mortality can be decreased through the endoscopic removal of adenomatous polyps, the question remains as to whether further endoscopic surveillance is necessary after polypectomy and, if so, how often. The most recent iteration of the United States Multi-Society Task Force guidelines endorsed a lengthening of the surveillance interval following the removal of low-risk adenomas (LRAs), defined as one to two tubular adenomas <10 mm with low-grade dysplasia, while maintaining a shorter interval for high-risk adenomas (HRAs), defined as advanced adenomas (villous histology, high-grade dysplasia, or >10 mm) or more than three adenomas.



Dr. Ness

Dr. Duvvuri and colleagues present the results of a systematic review and meta-analysis of studies examining metachronous CRC incidence and mortality following index colonoscopy. They found a small but statistically significant increase in the incidence of CRC but no significant difference in CRC mortality when comparing patients with LRAs to those with no adenomas. In contrast, they found both a statistically and clinically significant difference in CRC incidence/mortality when comparing patients with HRAs to both those with no adenomas and those with LRAs. They concluded that these results support a recommendation for no difference in follow-up surveillance between patients with LRAs and no adenomas but do support more frequent surveillance for patients with HRAs at index colonoscopy.

Future studies should better examine the timing of neoplasm incidence/recurrence following adenoma removal and also examine metachronous CRC incidence/mortality in patients with sessile serrated lesions at index colonoscopy.

Reid M. Ness, MD, MPH, AGAF, is an associate professor in the division of gastroenterology, hepatology, and nutrition at Vanderbilt University Medical Center and at the VA Tennessee Valley Healthcare System, Nashville, campus. He is an investigator in the Vanderbilt-Ingram Cancer Center. Dr. Ness has no financial relationships to disclose.

Lasting norovirus immunity may depend on T cells

BY WILL PASS

Protection against norovirus gastroenteritis is supported in part by norovirus-specific CD8+ T cells that reside in peripheral, intestinal, and lymphoid tissues, according to investigators.

These findings, and the molecular tools used to discover them, could guide development of a norovirus vaccine and novel cellular therapies, according to lead author Ajinkya Pattekar, MD, of the University of Pennsylvania, Philadelphia, and colleagues.

"Currently, there are no approved pharmacologic therapies against norovirus, and despite several promising clinical trials, an effective vaccine is not available," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology (2021 Jan 11;11[5]:1267-89), which may stem from an incomplete understanding of norovirus immunity, according to Dr. Pattekar and colleagues.

They noted that most previous research has focused on humoral immunity, which appears variable between individuals, with some people exhibiting a strong humoral response, while others mount only partial humoral protection. The investigators also noted that, depending on which studies were being examined, this type of defense could last years or it could last within only weeks or months and that "immune mechanisms other than antibodies may be important for protection against noroviruses."

Specifically, cellular immunity may be at work. A 2020 study involving volunteers showed that T cells were cross-reactive to a type of norovirus the participants had never been exposed to (Cell Mol Gastroenterol Hepatol. 2020;10[2]:245-67).

"These findings suggest that T cells may target conserved epitopes and could offer cross-protection against a broad range of noroviruses," Dr. Pattekar and colleagues wrote.

To test this hypothesis, they first collected peripheral blood mononuclear cells (PBMCs) from three healthy volunteers with unknown norovirus exposure history. Then serum samples were screened for norovirus functional antibodies via the binding between virus-like particles (VLPs) and histo–blood group antigens (HBGAs). This revealed disparate profiles of blocking antibodies against various norovirus strains. While donor 1 and donor 2 had antibodies against multiple strains, donor 3 lacked norovirus antibodies. Further testing showed that this latter individual was a nonsecretor with limited exposure history.

Next, the investigators tested donor PBMCs for norovirus-specific T-cell responses with use of overlapping libraries of peptides for each of the three norovirus open reading frames (ORF1, ORF2, and ORF3). T-cell responses, predominantly involving CD8+ T cells, were observed in all donors. While donor 1 had the greatest response to ORF1, donors 2 and 3 had responses that focused on ORF2.

"Thus, norovirus-specific T cells targeting ORF1 and ORF2 epitopes are present in peripheral blood from healthy donors regardless of secretor status," the investigators wrote.

To better characterize T-cell epitopes, the investigators subdivided the overlapping peptide libraries into groups of shorter peptides, then exposed serum to these smaller component pools. This revealed eight HLA class I restricted epitopes that were derived from a genogroup II.4 pandemic norovirus strain; this group of variants has been responsible for all six of the norovirus pandemics since 1996.

Closer examination of the epitopes showed that they were "broadly conserved beyond GII.4." Only one epitope exhibited variation in the C-terminal aromatic anchor, and it was nondominant. The investigators therefore identified seven immunodominant CD8+ epitopes, which they considered "valuable targets for vaccine and cell-based therapies.

"These data further confirm that epitope-specific CD8+ T cells are a universal feature of the overall norovirus immune response and could be an attractive target for future vaccines," the investigators wrote.

Additional testing involving samples of spleen, mesenteric lymph nodes, and duodenum from deceased individuals showed presence of norovirus-specific CD8+ T cells, with particular abundance in intestinal tissue, and distinct phenotypes and functional properties in different tissue types.

"Future studies using tetramers and intestinal samples should build on these observations and fully define the location and microenvironment of norovirus-specific T cells," the investigators wrote. "If carried out in the context of a vaccine trial, such studies could be highly valuable in elucidating tissue-resident memory correlates of norovirus immunity."

The study was funded by the National Institutes of Health, the Wellcome Trust, and Deutsche Forschungsgemeinschaft. The investigators reported no conflicts of interest.

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Daisy-Daisy/iStock/Getty Images

Understanding the immune correlates of protection for norovirus is important for the development and evaluation of candidate vaccines and to better clarify the variation in host susceptibility to infection.

Dr. Wilen

Prior research on the human immune response to norovirus infection has largely focused on the antibody response. There is less known about the antinorovirus T-cell response, which can target and clear virus-infected cells. Notably, anti-viral CD8+ T cells are critical for control of norovirus infection in mouse models, which suggests a similarly important role in humans. In this study by Dr. Pattekar and colleagues, the authors generated human norovirus-specific peptides covering the entire viral proteome, and then they used these peptides to identify and characterize norovirus-specific CD8+ T cells from the blood, spleen, lymph nodes, and intestinal lamina propria of human donors who were not actively infected by norovirus. The authors identified virus-specific memory T cells in the blood and intestines. Further, they found several HLA class I restricted virus epitopes that are highly conserved amongst the most commonly circulating GII.4 noroviruses. These norovirus-specific T cells represented about 0.5% of all cells and reveal that norovirus induces a durable population of memory T cells.

Further research is needed to determine whether norovirus-specific CD8+ T cells are necessary or sufficient for preventing norovirus infection and disease in people. This important study provides novel tools and increases our understanding of cell-mediated immunity to human norovirus infection that will influence future vaccine design and evaluation for this important human pathogen.

Craig B. Wilen, MD, PhD, is assistant professor of laboratory medicine and immunobiology at Yale University, New Haven, Conn. He does not have any conflicts to disclose.

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Automated software accurately generates ERCP quality reports

BY WILL PASS

Modified endoscopy documentation software can automatically generate endoscopic retrograde cholangiopancreatography (ERCP) quality metrics, based on a trial at two referral centers.

Providers were prompted as they worked through procedures, and inputting any missed data took providers less than 30 additional seconds per patient. The approach led to highly accurate quality reports, lead author Gregory A. Coté, MD, MS, AGAF, of the Medical University of South Carolina, Charleston, and colleagues wrote in Techniques and Innovations in Gastrointestinal Endoscopy (2021 Jan 17. doi: 10.1016/j.tige.2021.01.005).

"If applied to a national cohort, this tool could accurately assess the current landscape of ERCP quality and provide tremendous opportunities for systematic improvement."

The investigators suggested that these findings may lead to the kind of quality reports already used for colonoscopy, which have been easier to produce. Such reports are important, they wrote, with the U.S. health care system shifting to value-based reimbursement models; these models in turn put greater scrutiny on the quality of endoscopic procedures. However, doing so with ERCP isn't entirely straightforward.

"Measuring adherence to ERCP quality indicators is especially challenging given: variance in indications, intraprocedural maneuvers, potential outcomes of a complex procedure, and variability in physician report documentation," Dr. Coté and colleagues wrote. "In order to operationalize robust tracking of clinically relevant adherence to ERCP quality indicators in clinical practice – that is, to provide real-time feedback to providers, health systems, payors, and patients – an automated system of measurement must be developed."

The quality indicators used in the study were largely drawn from an American Society for Gastrointestinal Endoscopy/American College of Gastroenterology task force document (Gastrointest Endosc. 2015 Jan;81[1]:54-66), with exclusion of those that were subjective or required systematic follow-up.

The investigators modified existing endoscopy documentation software at two referral centers to include mandatory, structured data fields, principally with inclusion of quality improvements deemed high priority by the society consensus document, study authors, or both. For instance, providers were obligated to select a specific indication instead of various, synonymous terms (for example, "biliary stricture" vs. "common bile duct stricture"). Examples of quality indicators included successful cannulation of the desired duct, successful retrieval of stone less than 10 mm, or successful placement of a bile duct stent when indicated. Endoscopists were also required to note the presence of postoperative foregut anatomy or presence of existing sphincterotomy, variables which serve to stratefy the quality indicator outcome for degree of difficulty and allow appropriate comparisons of data. In addition, the study authors included inquiries about use of rectal indomethacin, use of prophylactic pancreatic duct stent, and documentation of need for repeat ERCP, follow-up x-ray, or both.

After 9 months, the system recorded 1,376 ERCP procedures conducted by eight providers, with a median annualized volume of 237 procedures (range, 37-336). Almost one-third (29%) of the patients had not had prior sphincterotomy.

Automated reporting of ERCP was compared with manual record review, which confirmed high (98%-100%) accuracy. This high level of accuracy "obviates the need for manual adjudication of medical records," the investigators wrote.

They used data from one provider to create a template report card, and while exact comparisons across providers and institutions were not published, the study included an example report card that did show how such comparisons could be generated in the real world if tools like this one were implemented down the line.

"The tool presented in this study allows for an objective assessment of ERCP performance which can provide explicit feedback to providers and allow transparent assessment of quality outcomes; it has the potential to improve the quality of ERCP akin to what has been demonstrated using colonoscopy report cards," the investigators wrote. "Importantly, this can be achieved with minimal alteration to providers' routine procedure documentation."

Dr. Coté and colleagues also noted that the software modifications "can be implemented in other endoscopy units using the same or similar software."

Taking the project to the next level would require widespread collaboration, according to the investigators.

"A key next step is to operationalize the transfer of data across multiple institutions, allowing for the creation of interim, standard-quality indicator reports that could be disseminated to providers, health systems, and payors," they wrote.

"If applied to a national cohort, this tool could accurately assess the current landscape of ERCP quality and provide tremendous opportunities for systematic improvement," they added.

One author disclosed a relationship with Provation Medical, but the remaining authors declared no relevant conflicts.

ginews@gastro.org

Quality indicators have been proposed to improve the outcome of patients undergoing endoscopic procedures. The path toward quality improvement begins with selection of parameters, which matters a great deal and have wide performance variation. Endoscopists then track their own performance, compare it with targets based on community standards, and improve their patients' outcomes using this feedback. Great progress has been made in the area of tracking and improving adenoma detection rate, an indicator closely tied to reduction in colorectal cancer mortality.

Dr. Cohen

Endoscopic retrograde cholangiopancreatography (ERCP) is a high-stakes procedure with great potential therapeutic benefit and with a small but significant risk of life-threatening complications such as pancreatitis. This study by Coté and colleagues illuminates an effective and straightforward step to making ERCP quality improvement feasible. The report card concept is not new, but the novel innovation is to leverage the use of required fields in the electronic report generator. Seamlessly, this produces nuanced reports that link provider performance to patient characteristics and indication.

The authors have shown extremely high accuracy of automatic electronic ERCP quality indicator recording, compared with manual data collection. Such data have clear and immediate utility in the credentialing process and quality improvement arena. With this means of recording outcomes, deidentified ERCP quality data might soon join colonoscopy data in national data repositories such as the GI Quality Improvement Consortium, and government quality reporting on ERCP outcomes would become much more feasible. Fellow self-assessment and logging of progress could also be facilitated if report generators were further amended to require recording of fellow participation.

Jonathan Cohen, MD, FASGE, is a clinical professor of medicine at New York University Langone Health. He reported having no relevant conflicts of interest.

AGAF applications now open

Applications are now open for the 2022 AGA Fellowship cohort. AGA is proud to formally recognize its exemplary members whose accomplishments and contributions demonstrate a deep commitment to gastroenterology through the AGA Fellows Program. Those in clinical practice, education or research (basic or clinical) are encouraged to apply today.

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Make a tribute gift to honor someone whose life has been touched by GI research or celebrate a special occasion such as a birthday while supporting the AGA Research Awards Program through the AGA Research Foundation. A tribute gift will make your loved one feel special because it honors their passion, and also help us fund research grants to talented investigators whose work will shape the future of clinical care.

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Learn more about ways to recognize and acknowledge someone by visit our website at https://foundation.gastro.org/ways-to-contribute/.

➤ GI ONCOLOGY

Age should not be a barrier to esophageal cancer treatment

BY M. ALEXANDER OTTO

Neoadjuvant chemoradiation plus esophagectomy can be performed safely in well-selected older patients with locally advanced esophageal or esophagogastric junction cancer, according to a review of 282 patients treated from 2004 through 2019 at Ochsner Medical Center, New Orleans (J Am Coll Surg. 2021;S1072-7515[20]32581-3).

Although guidelines recommend curative-intent neoadjuvant chemoradiation (NACR) followed by surgical resection, it's been demonstrated in several studies that "older patients with potentially curable stage II and III disease are often not considered" for the approach out of concern that they will not tolerate it, said investigators led by W. Peter Sawyer, MD, a surgery resident at Ochsner.

Outcomes, however, were comparable in the study when 188 patients aged younger than 70 years were compared with 94 patients aged 70 years or older, including 4 who were over 80 years old. "Patients 70 years and older should be evaluated for optimal curative therapy including neoadjuvant chemoradiotherapy and surgical resection," the investigators concluded.

The patients had NACR followed by esophagectomy mostly for stage II disease. The average age was 59 years in the younger group and 74 years in the older group. The team noted that the results "reflect careful patient selection as well as thorough preoperative evaluation and preparation."

There was no outside funding. Investigator disclosures weren't reported.

aotto@mdedge.com

Blood test detects precancerous colorectal adenomas

ROXANNE NELSON, RN, BSN

A novel blood test has shown promise for colorectal cancer screening.

The "multiomics" test, under development by Freenome, has previously been shown to detect early-stage (I/II) colorectal cancer with a sensitivity of 94% and a specificity of 94%.

A new study shows that it can also detect precancerous lesions, colorectal advanced adenomas (AAs).

"The ability to detect advanced adenomas is incredibly important because we can remove them before they become cancerous," senior author Aasma Shaukat, MD, MPH, AGAF, chief of gastroenterology at Minneapolis VA Health Care System and professor of medicine at the University of Minnesota, Minneapolis, said in a statement.

The new test had almost double the sensitivity for detecting AAs as the fecal immunochemical test, and its sensitivity was comparable to that of FIT-DNA testing.

At the Gastrointestinal Cancers Symposium 2021, she presented data showing that the novel test was able to detect AAs with a sensitivity of 41% and a specificity of 90%.

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.

This sensitivity of the new test is better than or similar to that of currently available stool tests, noted study author C. Jimmy Lin, MD, PhD, MHS, chief scientific officer at Freenome.

The new test had almost double the sensitivity for detecting AAs (41% vs. 24%) as the fecal immunochemical test (FIT), and its sensitivity was comparable to that of FIT-DNA testing (41% vs. 42%).

In addition, it showed much higher sensitivity (41% vs 22%) for detecting AAs than the Epi proColon, a screening blood test that has been approved by the U.S. Food and Drug Administration for detecting methylated septin 9 DNA (mSEPT9).

Their platform integrates assays for circulating free DNA, methylation, and proteins using advanced computational biology and machine-learning techniques, which provide a multidimensional view of both tumor- and immune-de-

Continued on following page

When should antibiotics be used in acute uncomplicated diverticulitis?

Think carefully about when to withhold

Among generally healthy patients with an initial diagnosis of acute uncomplicated diverticulitis, about 3% will progress to complicated diverticulitis, and about 1% will require emergency surgery within 6 months. Around another 6% of cases will develop chronic diverticulitis with ongoing diverticular inflammation that persists for weeks to months. Knowing the possibility of these complications, many physicians prescribe antibiotics for acute uncomplicated diverticulitis to prevent a bad outcome. Because the complications are uncommon, we don't know if antibiotics reduce the risk of progression to complicated diverticulitis, emergency surgery, or the development of chronic diverticulitis. With little evidence for or against antibiotics, recent guidelines have begun to recommend that antibiotics be used selectively, rather than routinely, in patients with diverticulitis. "Selectively" clearly means that there are some patients who should receive antibiotics, but the guidelines are vague about who those patients are. To implement this recommendation, physicians must therefore identify which patients are at the greatest risk of developing a complication. To this end, it is safest to refer back to small, underpowered trials evaluating antibiotics for patients with acute uncomplicated diverticulitis. The authors of those trials considered a number of groups high risk and, therefore, excluded them from those trials. In the absence of further definitive research, it seems clear that those groups should be selected for antibiotic treatment. Avoiding antibiotics requires shared decision-making with a well-informed patient. I have patients who have embraced this approach, while others found this unacceptable. Given the current level of uncertainty in the literature, I offer antibiotics to any patient who feels strongly about receiving them.

Dr. Peery

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

Anne F. Peery, MD, MSCR, is with the center for gastrointestinal biology and disease at the University of North Carolina, Chapel Hill. She has no conflicts to disclose.

The data are robust for withholding more often

That we are engaged in a legitimate debate about the role of antibiotics in acute uncomplicated diverticulitis is itself quite notable. In the 1999 American College of Gastroenterology practice guidelines, we did not even entertain the concept of withholding antibiotics; the only discussion points were intravenous versus oral. Fast forward 15 years, and in the 2015 American Gastroenterological Association practice guidelines (which Dr. Peery and I worked on together) our first recommendation was that antibiotics should be used "selectively," rather than routinely. This did generate some raised eyebrows and hand-wringing in the community, but our position was the result of a rigorous data-analysis process and we stood by it.

Dr. Stollman

In fact, Dr. Peery and I also coauthored an accompanying editorial that concluded with an important endorsement "allowing the clinician to consider withholding antibiotics from select uncomplicated patients with mild disease." I suspect, then, that Dr. Peery and I are very much coincident in our overall thoughts here, and I'm pretty sure that neither of us would defend an "always" or "never" stance on this issue, so for this educational debate, we're really talking about where in the middle to draw the line (that is, how to define "selectively"). To that end, I will defend the supposition that the subsequent data in support of withholding antibiotics remain robust and even more supportive of this practice in many (but certainly not all) patients with acute, uncomplicated diverticulitis.

Neil Stollman, MD, AGAF, FACG, is chairman of the division of gastroenterology at Alta Bates Summit Medical Center in Oakland, Calif., and an associate clinical professor of medicine in the division of gastroenterology at the University of California, San Francisco. He discloses being a consultant for Cosmo Pharmaceuticals, which has a potential future diverticulitis study of a rifampin-class antibiotic.

Dear colleagues and friends,
The Perspectives series returns, this time with an exciting discussion about antibiotic use in acute uncomplicated diverticulitis. It has been fascinating to witness this field evolve from an era where not using antibiotics was inconceivable! Dr. Anne F. Peery and Dr. Neil Stollman, both recognized experts in the matter, provide arguments to both sides of the debate, as well as much-needed nuance. As always, I welcome your comments and suggestions for future topics at ginews@gastro.org. Thank you for your support, and I hope you will enjoy reading and learning from this as much as I did.

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

Dr. Kahi

Continued from previous page

rived signatures that enable the early detection of cancer.

Better sensitivity

The study presented at the meeting evaluated the novel multiomics blood test for AA detection.

Blood samples were obtained from participants in the AI-EMERGE study, a prospective, multicenter study that included primarily average-risk screening patients from 30 clinical sites in the United States and Canada. The study included a total of 542 samples, including 122 histopathologically confirmed AAs and 420 colonoscopy-confirmed negative control samples.

"By combining signatures from both tumor and non–tumor-derived sources, our multiomics signatures detect twice as many AAs as methylation-only or single-protein approaches," Dr. Lin said. "And we have now shown that sensitive AA detection at a level similar to or better than currently available stool tests is achievable in blood, which is necessary for effective early detection and prevention of colorectal cancers."

The company has begun the regulatory process for having the test approved by the FDA. The company's goal is to enroll 14,000 participants and have prospectively collected data.

The research was funded by Freenome. Dr. Lin is the chief scientific officer at Freenome and has relationships with Labroots, Natera, and Neon Therapeutics. Shaukat has relationships with Freenome and Iterative Scopes.

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

Newer models have proven safer

Balloons *from page 1*

obesity (body mass index >30 kg/m^2), placing an intragastric balloon (IGB) significantly improved key outcomes such as weight loss, metabolic parameters (such as fasting blood glucose, hemoglobin A1c), and rates of remission of diabetes, hypertension, and dyslipidemia, compared with standard noninvasive weight-loss interventions, Thiruvengadam Muniraj, MD, MRCP, of Yale University in New Haven, Conn., and associates wrote in Gastroenterology (2021 Apr 1;160[5]:1799-808). However, concomitant lifestyle modifications of "moderate to high intensity" are strongly recommended "to maintain and augment weight loss" after IGB placement, according to the guidelines published in Gastroenterology.

Obesity (BMI >30 kg/m^2) affects approximately 40% of U.S. adults, but only about 1.1% of eligible patients receive bariatric weight-loss surgery, and few are aware that endoscopic treatment is an option.

Obesity (BMI >30), affects approximately 40% of U.S. adults, but only about 1.1% of eligible patients receive bariatric weight-loss surgery, and few are aware that endoscopic treatment is an option, according to the guideline. Early IGB models were associated with "a number of devastating adverse events," spurring their removal from the U.S. market in the 1980s and 1990s.

Since then, however, several new models of IGBs have become available. The guidelines noted that, in seven randomized, controlled trials of these newer IGBs, there were no deaths and only a 5.6% overall rate of serious adverse events – most commonly injury to the gastrointestinal tract at 6-8 months' follow-up. "More recently, postmarketing surveillance of IGB has reported additional rare adverse events of hyperinflation, acute pancreatitis, and death," but overall, "IGBs appear to be associated with both a favorable adverse event and patient tolerability profile."

There are three models of fluid-filled balloons and two models of gas-filled balloons that are currently available in the United States, the guidelines noted. The authors did not recommend one specific type or model over another. They cite limited data indicating that "fluid-filled balloons may be associated with more weight loss, lower tolerability, and less favorable safety profile, than gas filled balloons. Shared decision-making is suggested for determining device choice."

Relatively few studies have evaluated lifestyle modifications after IGB placement. In one study of 80 patients, a very-low-calorie ketogenic diet led to significantly more weight loss (on average, 7.1 kg), compared with a conventional low-calorie diet (Obes Surg. 2018 Dec;28[12]:3733-7).

"Although diet does augment and sustain weight loss in patients receiving IGB therapy, it is unclear whether other lifestyle modifications (e.g., exercise) would have the same impact," the guideline authors wrote.

They strongly recommended prophylactic proton pump inhibitor (PPI) therapy after IGB placement. The procedure can erode the gastrointestinal mucosa, and studies in which patients received prophylactic PPIs reported lower rates of serious adverse events, most notably upper GI bleeding. However, the numerous short- and long-term risks of these drugs make it "imperative that the lowest dose, frequency, and duration of PPIs be used in patients undergoing IGB therapy."

Intragastric balloons can cause nausea and vomiting, leading to their premature removal. Therefore, when placing an IGB, concomitant antiemetic therapy is recommended along with an anesthetic that is unlikely to cause nausea. "Evidence is insufficient to recommend a specific antiemetic regimen" and "choice of regimen [should be] based on institutional policy, clinical context, and availability," according to the guidelines.

Based on low-quality evidence, they included a conditional recommendation for daily vitamin supplementation with one to two adult-dose multivitamins after IGB placement. They suggest against perioperative laboratory screening for nutritional deficiencies, based on a lack of supporting evidence. However, since nutritional deficiencies with IGB placement have been reported, decisions about screening for nutritional deficiencies should be tailored based on clinical judgment.

To create the guideline, the authors reviewed databases for studies published through January 2020 in which patients with obesity had an IGB placed for at least 6 months. In all, 79 articles were cited, including more than 10 randomized clinical trials. An update of the clinical practice guidelines is expected in 2024.

The AGA Institute provided the only funding. Dr. Muniraj and five coauthors reported having no conflicts of interest. The other two coauthors disclosed relationships with Nestle Health Sciences, the American Society for Gastrointestinal Endoscopy, the American College of Gastroenterology, and the Association of American Indian Physicians.

ginews@gastro.org

CLINICAL CHALLENGES AND IMAGES

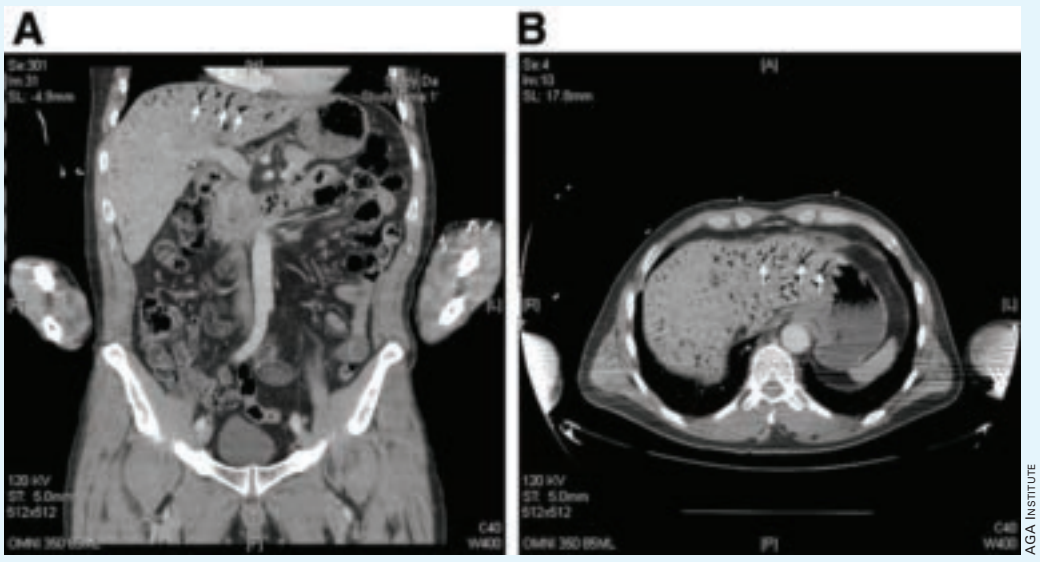
What's your diagnosis?

BY OSAMA DASA, MD, MPH; MORGAN K. MOROI, MD; AND MOHAMMED RUZIEH, MD

Published previously in Gastroenterology *(2019 Aug 1;157[2]:313-4).*

A 52-year-old man with no past medical or surgical history presented to the emergency department after accidental ingestion of 300 mL of a colorless liquid from his refrigerator. The patient instantly noticed a bitter taste in his mouth as well as burning sensation throughout his oropharynx and esophagus. Immediately after ingestion, the patient also experienced severe retching and emesis. On initial presentation, the patient was hemodynamically stable.

There was no evidence of pneumoperitoneum, nor cardiac or neurologic symptoms suggesting air embolism. A computed tomography (CT) scan of his abdomen and pelvis revealed the images displayed in Figure A, B. Further history revealed ingestion of unlabeled 35% hydrogen peroxide (H_2O_2).



How should this condition be managed?

The answer is on pg 34.

Update on dyssynergic defecation: Going beyond diagnosis

SATISH S.C. RAO, MD, PHD, AND ASAD JEHANGIR, MD

Introduction

About 40% of the population experiences lower GI symptoms suggestive of gastrointestinal motility disorders.[1,2] The global prevalence of chronic constipation is 18%, and the condition includes multiple overlapping subtypes.[3] Evacuation disorders affect over half (59%) of patients and include dyssynergic defecation (DD).[4] The inability to coordinate the abdominal, rectal, pelvic floor, and anal/puborectalis muscles to evacuate stools causes DD.[5] The etiology of DD remains unclear and is often misdiagnosed. Clinically, the symptoms of DD overlap with other lower GI disorders, often leading to unnecessary and invasive procedures.[2] We describe the clinical characteristics, diagnostic tools, treatment options, and evidence-based approach for the management of DD.

Clinical presentation

Over two-thirds of patients with DD acquire this disorder during adulthood, and one-third have symptoms from childhood.[6] Though there is not usually an inciting event, 29% of patients report that symptoms began after events such as pregnancy or back injury,[6] and opioid users have higher prevalence and severity of DD.[7]

Over 80% of patients report excessive straining, feelings of incomplete evacuation, and hard stools, and 50% report sensation of anal blockage or use of digital maneuvers.[2] Other symptoms include infrequent bowel movements, abdominal pain, anal pain, and stool leakage.[2] Evaluation of DD includes obtaining a detailed history utilizing the Bristol Stool Form Scale[8]; however, patients' recall of stool habit is often inaccurate, which results in suboptimal care.[9,10] Prospective stool diaries can help to provide more objective assessment of patients' symptoms, eliminate recall bias, and provide more reliable information. Several useful questionnaires are available for clinical and research purposes to characterize lower-GI symptoms, including the Constipation Scoring System,[11] Patient Assessment of Constipation Symptoms (PACSYM),[12] and Patient Assessment of Constipation Quality of Life (PACQOL).[2,13] The Constipation Stool digital app enhances accuracy of data capture and offers a reliable and user-friendly method for recording bowel symptoms for patients, clinicians, and clinical investigators.[14]

Diagnosis

The diagnosis of DD requires careful physical and digital rectal examination together with anorectal manometry and a balloon expulsion test. Defecography and colonic transit studies provide additional assessment.

Physical examination

Abdominal examination should include palpation for stool in the colon and identification of abdominal mass or fecal impaction.[2] A high-quality digital rectal examination can help to identify patients who could benefit from physiological testing to confirm and treat DD.[15] Rectal examination is performed by placing examiner's lubricated gloved right index finger in a patient's rectum, with the examiner's left hand on patient's abdomen, and asking the patient to push and bear down as if defecating.[15] The contraction of the abdominal muscles is felt using the left hand, while the anal sphincter relaxation and degree of perineal descent are felt using the right-hand index finger.[15] A diagnosis of dyssynergia is suspected if the digital rectal examination reveals two or more of the following abnormalities: inability to contract abdominal muscles (lack of push effort), inability to relax or paradoxical contraction of the anal sphincter and/or puborectalis, or absence of perineal descent.[15] Digital rectal examination has good sensitivity (75%), specificity (87%), and positive predictive value (97%) for DD.[16]

High-resolution anorectal manometry

Anorectal manometry (ARM) is the preferred method for the evaluation of defecatory disorders.[17,18] ARM is best performed using the high-resolution anorectal manometry (HRAM) systems[19] that consist of a flexible probe – 0.5-cm diameter with multiple circumferential sensors along the anal canal – and another two sensors inside a rectal balloon.[18] It provides a topographic and waveform display of manometric pressure data (Figure). The 3D high-definition ARM probe is a rigid 1-cm probe that provides 3D topographic profiles.[18] ARM is typically performed in both the left lateral position and in a more physiological seated position.[20,21] There is considerable variation amongst different institutions on how to perform HRAM, and a recent International Anorectal Physiology Working Group (IAPWG) has provided consensus recommendations for performing this test.[22] The procedure for performing HRAM is reviewed elsewhere, but the key elements are summarized below.[18]

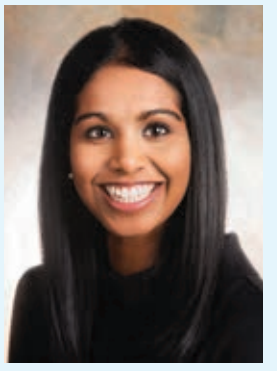
Push maneuver: On HRAM, after the assessment of resting and squeeze anal sphincter pressures, the patient is asked to push or bear down

Dr. Rao is J. Harold Harrison Distinguished University Chair, professor of medicine, director of neurogastroenterology/motility, and director of Digestive Health Clinical Research Center at Augusta (Ga.) University. Dr. Jehangir is a gastroenterology and Hepatology Fellow at the Digestive Health Clinical Research Center at Augusta University. They reported having no conflicts of interest.

One of the most frequently encountered gastrointestinal diagnoses is chronic constipation. Dyssynergic defecation (DD) is a common etiology that affects up to one-half of patients with chronic constipation. The pathophysiology and diagnostic modalities are often not well understood by trainees or by early-career gastroenterologists, which poses a barrier to the initiation of appropriate and timely treatment. The diagnosis of DD is complex and lies at the junction of a specific constellation of symptoms, physical exam findings, and relevant testing such as anorectal manometry, the balloon expulsion test, and defecography studies.

The In Focus article for May, which is brought to you by The New Gastroenterologist, provides an excellent, comprehensive review written by international expert Dr. Satish S. C. Rao and Dr. Asad Jehangir (both with Medical College of Georgia/Augusta University). The article provides guidance on diagnosing DD, including high-yield features of the digital rectal exams, as well as ways to interpret results from anorectal manometry and their clinical significance. Importantly, the authors lend clarity on how these studies dictate a therapeutic plan and, ultimately, improve patient care.

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

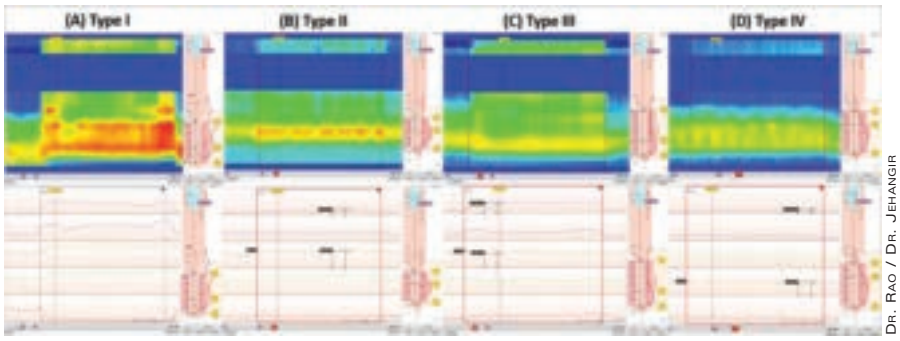


Dr. Rao

as if to defecate while lying in left lateral decubitus position. The best of two attempts that closely mimics a normal bearing down maneuver is used for categorizing patient's defecatory pattern.[18] In patients with DD, at least four distinct dyssynergia phenotypes have been recognized (Figure),[23] though recent studies suggest eight patterns.[24] Defecation index (maximum rectal pressure/minimum residual anal pressure when bearing down) greater than 1.2 is considered normal.[18]

Simulated defecation on commode: The subject is asked to attempt defecation while seated on a commode with intrarectal balloon filled with 60 cc of air, and both the defecation pattern(s) and defecation index are calculated. A lack of coordinated push effort is highly suggestive of DD.[21]

Rectoanal Inhibitory Reflex (RAIR): RAIR describes the reflex relaxation of the internal anal sphincter after rectal distension. RAIR is dependent on intact autonomic ganglia and myenteric plexus[25] and is mediated by the release of nitric oxide and vasoactive intestinal peptide.[26] The absence of RAIR suggests Hirschsprung disease.[22,27,28]



Dr. Rao / Dr. Jehangir

Figure - Manometrically there are four different types of DD. (A) The patient with Type I DD is able to generate an adequate propulsive force but with a paradoxical increase in anal sphincter pressure. (B) The patient with Type II DD is unable to generate an adequate propulsive force and paradoxically increases the anal sphincter pressure. (C) The patient with Type III DD is able to generate an adequate propulsive force, with absent or incomplete (< 20%) anal sphincter relaxation. (D) The patient with Type IV DD is unable to generate an adequate propulsive force with absent or incomplete anal sphincter relaxation.

Rectal sensory testing: Intermittent balloon distension of the rectum with incremental volumes of air induces a range of rectal sensations that include first sensation, desire to defecate, urgency to defecate, and maximum tolerable volume. Rectal hyposensitivity is diagnosed when two or more sensory thresholds are higher than those seen in normal subjects[29,30] and likely results from disruption of afferent gut-brain pathways, cortical perception/rectal wall dysfunction, or both.[29] Rectal hyposensitivity affects 40% of patients with constipation[30] and is associated with DD but not delayed colonic transit.[31] Rectal hyposensitivity may also be seen in patients with diabetes or fecal incontinence.[18] About two-thirds of patients with rectal hyposensitivity have rectal hypercompliance, and some have megarectum.[32] Some patients with DD have coexisting irritable bowel syndrome (IBS) and may have rectal hypersensitivity.[18,33] Rectal compliance is measured alongside rectal sensitivity analysis by plotting a graph between the change in intraballoon volume (mL) and change in intrarectal pressures (mm Hg) during incremental balloon distensions.[18,34] Rectal hypercompliance may be seen in megarectum and dyssynergic defecation.[34,35] Rectal hypocompliance may be seen in patients with inflammatory bowel disease, postpelvic radiation, chronic ischemia, and advanced age.[18]

Balloon expulsion test: This test is performed by placing a plastic probe with a balloon in the rectum and filling it with 50 cc of warm water. Patients are given 5 minutes to expel the balloon while sitting on a commode. Balloon expulsion time of more than 1 minute suggests a diagnosis of DD,[21] although 2 minutes provides a higher level of agreement with manometric findings.[36] Balloon type and body position can influence the results.[37] Inability to expel the balloon with normal manometric findings is considered an inconclusive finding per the recent London Classification (i.e., it may be associated with generation of anorectal symptoms, but the clinical relevance of this finding is unclear as it may also be seen in healthy subjects).[22]

Defecography
Defecography is a dynamic fluoroscopic study performed in the sitting position after injecting 150 mL of barium paste into the patient's rectum. Defecography provides

Continued on following page

Randomized controlled studies of biofeedback therapy for dyssynergic defecation

Study	Trial design (n)	Technique	Primary outcome	Loss to follow-up	Follow-up	Result
Chiarioni[48]	Biofeedback (54) vs. polyethylene glycol (55)	EMG, five weekly, 30-minute sessions	Global symptom improvement	2/54 (3.7%) vs. 4/55 (7.3%)	24 months	• Favor biofeedback therapy • Major global symptom improvement 80% vs. 22% ($P < .01$) • More pelvic floor relaxation, improved balloon evacuation and urge threshold with biofeedback therapy vs. polyethylene glycol ($P < .01$)
Heymen[49]	Biofeedback (30) vs. diazepam (30) or placebo pill (24)	EMG, six biweekly, 50-minute sessions	Adequate relief of constipation	7/20 (23.3%), 7/30 (23.3%), 4/24 (16.7%)	3 months	• Favor biofeedback • Adequate relief of constipation 70% vs. 23% and 38% ($P < .01$) • More pelvic floor relaxation with biofeedback vs. diazepam or placebo ($P = .001$)
Rao[50]	Biofeedback (28) vs. sham feedback (25) or standard treatment (24)	Manometry, six biweekly, 60-minute sessions	CSBMs, global bowel satisfaction	7/28 (25%), 4/25 (16%), 1/23 (4.3%)	3 months	• Favor biofeedback • Global bowel satisfaction 75% vs. 48% and 63% ($P < .01$) • Higher CSBMs ($P < .05$), corrected dyssynergia ($P < .0001$), improved defecation index ($P < .0001$), and decreased BET ($P < .05$) vs. sham or standard treatment
Faried[62]	Biofeedback (24) vs. botulinum injection 500 unit (24)	EMG, eight biweekly sessions, duration not defined	Not clearly defined	3/24 (12.5% vs. 0%)	1 year	• Similar efficacy • Overall satisfaction 25% vs. 33% ($P < .05$) • Both treatments significantly improved dyssynergic pattern and BET but were not significantly different between groups
Rao[51]	Biofeedback (13) vs. standard therapy (13)	Six active therapy sessions and three reinforcement sessions at 3-month intervals	CSBMs, correction of dyssynergia, BET, global satisfaction	0% vs. 6/13 (46%)	1 year	• Favor biofeedback • CSBMs increased significantly in biofeedback therapy ($P < .001$), dyssynergia pattern normalized ($P < .001$), BET improved and colonic transit normalized ($P < .01$)
Simón[47]	Biofeedback (10) vs. counseling sessions (10) in community-dwelling elderly women (mean age, 74 years; range, 69-81 years)	EMG eight biweekly, 45-minute sessions	Clinical and physiological parameters	0%	3 months	• Favor biofeedback • Significant improvement in stool frequency, sensation of incomplete evacuation, and difficulty evacuation, as well as mean EMG-activity of the external anal sphincter and the anismus index
Rao[59]	Home biofeedback (50) vs. office biofeedback (50)	Home device 20 minutes, twice daily vs. manometry six biweekly 60-minute sessions	≥1 CSBM plus correction of dyssynergia	12/50 (24%) in home and 5/50 (10%) in office biofeedback	3 months	Home and office significant improvement. Home (68%) equally efficacious as office biofeedback (70%)

MDEdge News

Notes: Adapted from Patcharatrakul[52]. BET = balloon expulsion time, CSBMs = complete spontaneous bowel movements, EMG = electromyography.
Source: Dr. Rao, Dr. Jehangir

Large study for capsule-camera in the works

BY LIAM DAVENPORT

A miniature camera the size of a capsule that is swallowed and then transmits images of the inside of the gut can reveal cancer and gastrointestinal diseases. The device, which will be studied in a trial conducted by the National Health Service in England, is used by patients at home as a substitute for endoscopy.

The trial, announced on March 11, 2021, will initially involve 11,000 patients from 40 regions in England. Participants will be sent the colon capsule endoscopy to use at home. The capsule typically takes 5-8 hours to pass through the digestive system. As the capsule passes through the bowel, images are sent to a data recorder in a shoulder bag. The trial is being conducted by the University College London Hospitals NHS Foundation Trust. The investigators have created a guide on using the device at home.

The move is in response to a surge in patients coming forward for cancer checks after the slowdown in cancer services caused by the COVID-19 pandemic. In December 2020, more than 200,000 people came forward, an increase of 13,000 over the same month the previous year.

Traditional endoscopy services are still being offered, although endoscopies take longer to conduct because of infection control measures that must be employed to ensure that patients who undergo endoscopies do not develop COVID-19.

No funding for the study has been disclosed. No relevant financial relationships have been disclosed.

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

Continued from previous page

useful information about structural changes (e.g., rectoceles, enteroceles, rectal prolapse, and intussusception), DD, and descending perineum syndrome.[38] Methodological differences, radiation exposure, and poor interobserver agreement have limited its wider use; therefore, anorectal manometry and the balloon expulsion test are recommended for the initial evaluation of DD.[39] Magnetic resonance defecography may be more useful.[17,38]

Colonic transit studies

Colonic transit study can be assessed using radiopaque markers, wireless motility capsule, or scintigraphy. Wireless motility capsule and scintigraphy have the advantage of determining gastric, small-bowel, and whole-gut transit times as well. About two-thirds of patients with DD have slow transit constipation (STC),[6] which improves after treatment of DD.[40] Hence, in patients with chronic constipation, evaluation and management of DD is recommended first. If symptoms persist, then consider colonic transit assessment.[41] Given the overlapping nature of the conditions, documentation of STC at the outset could facilitate treatment of both.

Diagnostic criteria for DD

Patients should fulfill the following criteria for diagnosis of DD[42,43]:

- Fulfill symptom(s) diagnostic criteria for functional constipation and/or constipation-predominant IBS.
- Demonstrate dyssynergic pattern (Types I-IV; Figure) during attempted defecation on manometry recordings.

They should also meet one or more of the following criteria:

- Inability to expel an artificial stool (50 mL water-filled balloon) within 1 minute.
- Inability to evacuate or retention of 50% or more of barium during defecography. (Some institutions use a prolonged colonic transit time: greater than 5 markers or 20% or higher marker retention on a plain abdominal x-ray at 120 hours after ingestion of one radio-opaque marker capsule containing 24 radio-opaque markers.)

Treatment of DD

The treatment modalities for DD depend on several factors: patient's age, comorbidities, underlying pathophysiology, and patient expectations. Treatment options include standard management of constipation, but biofeedback therapy is the mainstay.

Standard management

Medications that cause or worsen constipation should be avoided. The patient should consume adequate fluid and exercise regularly. Patients should receive instructions for timed toilet training (twice daily, 30 minutes after meals). Patients should push at about 50%-70% of their ability for no longer than 5 minutes and avoid postponing defecation or use of digital maneuvers to facilitate defecation.[42] The patients should take 25 g of soluble fiber (e.g., psyllium) daily. Of note, the benefits of fiber can take days to weeks[44] and may be limited in patients with STC and DD.[45] Medications including laxatives and intestinal secretagogues (lubiprostone, linaclotide, plecanatide), and enterokinetic agents (prucalopride) can be used as adjunct therapy for management of DD.[42] Their use is titrated during and after biofeedback therapy and may decrease after successful treatment.[46]

Biofeedback therapy

Biofeedback therapy involves operant conditioning techniques using either a solid-state anorectal manometry system, electromyography, simulated balloon, or home biofeedback training devices.[42,47] The goals of biofeedback therapy are to correct the abdominal pelvic muscle discoordination during defecation and improve rectal sensation to stool if impaired. Biofeedback therapy involves patient education and active training (typically six sessions, 1-2 weeks apart, with each about 30-60 minutes long), followed by a reinforcement stage (three sessions at 3, 6, and 12 months), though there are variations in training protocols.[42]

The success of biofeedback therapy depends on the patient's motivation and the therapist's skills.[42] Compared with standard therapy (diet, exercise, pharmacotherapy), biofeedback therapy provides sustained improvement of bowel symptoms and anorectal function. Up to 70%-80% of DD patients show significant improvement of symptoms in randomized controlled trials (Table).[48-52]

Biofeedback therapy may also improve dyspeptic symptoms.[53] Patients with harder stool consistency, greater willingness to participate, lower baseline bowel satisfaction, lower baseline anal sphincter relaxation, and prolonged balloon expulsion time, as well as patients who used digital maneuvers for defection, more commonly respond to biofeedback therapy.[54,55] Longstanding laxative use has been associated with decreased response to biofeedback therapy.[56] In patients with rectal hyposensitivity, barostat-assisted sensory training is more effective than a hand-held syringe technique.[30] In patients with constipation-predominant IBS and rectal hyposensitivity, sensory adaption training is more efficacious and better tolerated than escitalopram.[30] Biofeedback therapy was afforded a grade A recommendation for treatment of DD by the American and European Societies of Neurogastroenterology and Motility.[57]

The access to office-based biofeedback therapy may be limited because of costs and low availability. The time required to attend multiple sessions may be burdensome for some patients, especially if they are taking time off from work. A recent study showed that patients with higher level of education may be less likely to adhere to biofeedback therapy.[58] Recently, home biofeedback was shown to be noninferior to office biofeedback and was more cost effective, which provides an alternative option for treating more patients.[59]

Endoscopic/surgical options

Other less effective treatment options for DD include botulinum toxin injection and myectomy.[60-62] Botulinum toxin injection appears to have mixed effects with less than 50% of patients reporting symptomatic improvement, and it may cause fecal incontinence.[60,63]

Conclusion

DD is a common yet poorly recognized cause of constipation. Its clinical presentation overlaps with other lower-GI disorders. Its diagnosis requires detailed history, digital rectal examination, prospective stool diaries, anorectal manometry, and balloon expulsion tests. Biofeedback therapy offers excellent and sustained symptomatic improvement; however, access to office-based biofeedback is limited, and there is an urgent need for home-based biofeedback therapy programs.[59]

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

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COVID-19 may alter gut microbiota

BY HEIDI SPLETE

COVID-19 infection altered the gut microbiota of adult patients and caused depletion of several types of bacteria with known immunomodulatory properties, based on data from a cohort study of 100 patients with confirmed COVID-19 infections from two hospitals.

"As the GI tract is the largest immunological organ in the body and its resident microbiota are known to modulate host immune responses, we hypothesized that the gut microbiota is associated with host inflammatory immune responses in COVID19," wrote Yun Kit Yeoh, PhD, of the Chinese University of Hong Kong, and colleagues.

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.

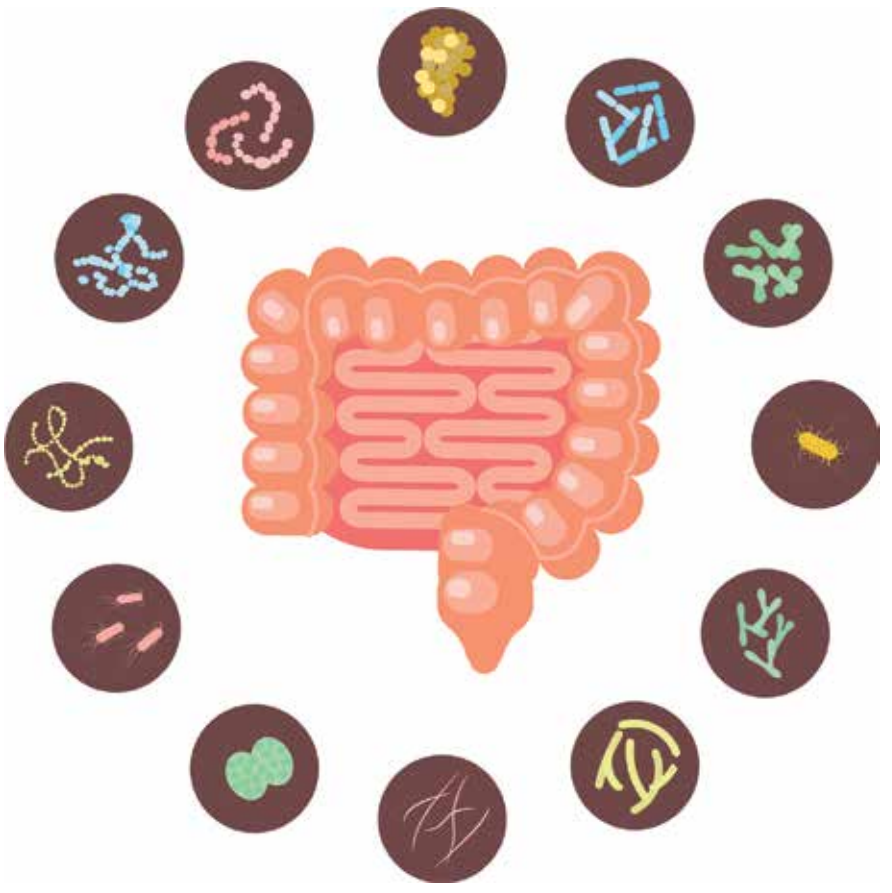
In a study published in Gut (2021 Jan 11. doi: 10.1136/gutjnl-2020-323020), the researchers investigated patient microbiota by collecting blood, stool, and patient records between February and May 2020 from 100 confirmed SARS-CoV-2–infected patients in Hong Kong during hospitalization, as well as follow-up stool samples from 27 patients up to 30 days after they cleared the COVID-19 virus; these observations were compared with 78 non–COVID-19 controls.

Overall, 274 stool samples were sequenced. Samples collected from patients during hospitalization for COVID-19 were compared with non–COVID-19 controls. The presence of phylum Bacteroidetes was significantly higher in COVID-19 patients compared with controls (23.9% vs. 12.8%; $P < .001$), as were Actinobacteria (26.1% vs. 19.0%; $P < .001$).

After controlling for antibiotics, the investigators found that "differences between cohorts were primarily linked to enrichment of taxa such as Parabacteroides, *Sutterella wadsworthensis*, and *Bacteroides caccae* and depletion of *Adlercreutzia equolifaciens*, *Dorea formicigenerans*, and *Clostridium leptum* in COVID-19 relative to non-COVID-19" ($P < .05$). In addition, *Faecalibacterium prausnitzii* and *Bifidobacterium bifidum* were negatively correlated with COVID-19 severity after investigators controlled for patient age and antibiotic use ($P < .05$).

The researchers also examined bacteria in COVID-19 patients and controls in the context of cytokines and other inflammatory markers. "We hypothesized that these compositional changes play a role in exacerbating disease by contributing to dysregulation of the immune response," they said.

In fact, species depleted in COVID-19 patients including *Bifidobacterium adolescentis*, *Eubacterium rectale,* and *F. prausnitzii* were negatively correlated with inflammatory markers including CXCL10, IL-10, TNF-alpha, and CCL2.



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In addition, 42 stool samples from 27 patients showed significantly distinct gut microbiota from controls up to 30 days (median, 6 days) after virus clearance, regardless of antibiotics use ($P < .05$), the researchers said.

Long-term data needed

The study findings were limited by several factors, including the potential confounding of microbial signatures associated with COVID-19 because of heterogeneous patient management in the clinical setting and the potential that gut microbiota reflects a patient's health with no impact on disease severity, as well as lack of data on the role of antibiotics for severe and critical patients, the researchers noted. In addition, "gut microbiota composition is highly heterogeneous across human populations and changes in compositions reported here may not necessarily be reflected in patients with COVID-19 from other biogeographies," they wrote.

The "longer follow-up of patients with COVID-19 (e.g., 3 months to 1 year after clearing the virus) is needed to address questions related to the duration of gut microbiota dysbiosis post recovery, link between microbiota dysbiosis and long-term persistent symptoms, and whether the dysbiosis or enrichment/depletion of specific gut microorganisms predisposes recovered individuals to future health problems," they wrote.

However, the results suggest a likely role for gut microorganisms in host inflammatory responses to COVID-19 infection, and "underscore an urgent need to understand the specific roles of gut microorganisms in human immune function and systemic inflammation," they concluded.

More than infectious

"A growing body of evidence suggests that severity of illness from COVID-19 is largely determined by the patient's aberrant immune response to the virus," Jatin Roper, MD, of Duke University, Durham, N.C., said in an interview. "Therefore, a critical question is: What patient factors determine this immune response? The gut microbiota closely interact with the host immune system and are altered in many immunological diseases," he said. "Furthermore, the SARS-CoV-2 virus infects enterocytes in the intestine and causes symptomatic gastrointestinal disease in a subset of patients. Therefore, understanding a possible association between gut microbiota and COVID-19 may reveal microbial species involved in disease pathogenesis," he emphasized.

In the current study, "I was surprised to find that COVID-19 infection is associated with depletion of immunomodulatory gut bacteria," said Dr. Roper. "An open question is whether these changes are caused by the SARS-CoV-2 virus and then result in altered immune response. Alternatively, the changes in gut microbiota may be a result of the immune response or other changes associated with the disease," he said.

"COVID-19 is an immunological disease, not just an infectious disease," explained Dr. Roper. "The gut microbiota may play an important role in the pathogenesis of the disease. Thus, specific gut microbes could one day be analyzed to risk stratify patients, or even modified to treat the disease," he noted.

Beyond COVID-19

"Given the impact of the gut microbiota on health and disease, as well as the impact of diseases on the microbiota, I am not at all surprised to find that there were significant changes in the microbiota of COVID-19 patients and that these changes are associated with inflammatory cytokines, chemokines, and blood markers of tissue damage," said Anthony Sung, MD, also of Duke University.

According to Dr. Sung, researchers have already been investigating possible connections between gut microbiota and other conditions such as Alzheimer's disease, and it's been hypothesized that these connections are mediated by interactions between the gut microbiota and the immune system.

"While this is an important paper in our understanding of COVID-19, and highlights the microbiome as a potential therapeutic target, we need to conduct clinical trials of microbiota-based interventions before we can fully realize the clinical implications of these findings," he said.

The study was supported by the Health and Medical Research Fund, the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region, and donations from Hui Hoy & Chow Sin Lan Charity Fund, Pine and Crane Company, Mr. Hui Ming, and The D.H. Chen Foundation. The researchers had no financial conflicts to disclose. Dr. Roper and Dr. Sung had no financial conflicts to disclose.

ginews@gastro.org

Listing is 'rife with impediments'

Minorities *from page 1*

toward improving and equalizing access to lifesaving organs for those on the liver transplant wait list, the listing process determining which patients will be considered for transplantation has continued to be a significant hurdle."

The process is "rife with impediments to equal access to listing," according to Dr. Warren and colleagues; getting on a waiting list can be affected by factors such as inequitable access to primary care, lack of private health insurance, and subjective selection by transplant centers.

To better characterize these impediments, the investigators gathered center-specific data from the Scientific Registry of Transplant Recipients and the U.S. Census Bureau. The final dataset included 30,353 patients treated at 109 transplant centers, each of which performed more than 250 transplants between January 2013 and December 2018. The investigators compared waiting list data for each center with demographics from its DSA. Primary variables included race/ethnicity, education level, poverty, and insurance coverage.

Multiple logistic regression analysis was used to compare expected waiting list demographics with observed waiting list demographics with the aid of observed/expected ratios for each race/ethnicity. Univariate and multivariate analyses were used to identify significant predictors, including covariates such as age at listing, distance traveled to transplant center, and center type.

On an adjusted basis, the observed/expected ratios showed that non-Hispanic Black patients were underrepresented on waiting lists at 88 out of 109 centers (81%) and Hispanic patients were underrepresented at 68 centers (62%). In contrast, non-Hispanic White patients were overrepresented on waiting lists at 65 centers (58%). Non-Hispanic White patients were underrepresented on waiting lists at 49 centers, or 45%. Minority

Dr. Nephew

Dr. Conteh

underrepresentation was further supported by mean MELD (Model for End-Stage Liver Disease) scores, which were significantly higher among non-Hispanic Black patients (20.2) and Hispanic patients (19.4), compared with non-Hispanic White patients (18.7) ($P < .0001$ for all) at the time of wait-listing.

Based on the multivariate model, underrepresentation among Black patients was most common in areas with a higher proportion of Black individuals in the population, longer travel distances to transplant centers, and a higher rate of private insurance among transplant recipients. For Hispanic patients, rates of private insurance alone predicted underrepresentation.

Once patients were listed, however, these disparities faded. Non-Hispanic Black patients accounted for 9.8% of all transplants across all hospitals, compared with 7.9% of wait-listed individuals ($P < .0001$). At approximately two out of three hospitals (65%), the transplanted percentage of Black patients exceeded the wait-listed percentage ($P = .002$).

"Data from this study show that the wait lists at many transplant centers in the United States underrepresent minority populations, compared with what would be expected based on their service areas," the investigators concluded. "Future work will need to be devoted to increasing awareness of these trends to promote equitable access to listing for liver transplantation."

Looking at social determinants of health

According to Lauren D. Nephew, MD, MSc, MAE, of Indiana University, Indianapolis, and not part of the study, "The question of access to care is particularly important at this juncture as we examine the inequities that COVID-19 exposed in access to care for racial minorities, and as we prepare for potential changes to health insurance coverage with the new administration."

Dr. Nephew noted that the reported racial disparities stem from social determinants of health, such as proximity to transplant centers and type of insurance coverage.

"Another striking finding was that the disparity in wait-listing non-Hispanic Black patients increased with the percentage of non-Hispanic Black patients living in the area, further highlighting barriers in access to care in majority Black neighborhoods," she said. "Inequities such as these are unacceptable, given our mandate to distribute organs in a fair and equitable fashion, and they require prospective studies for further examination."

Identifying discrimination

Lanla Conteh, MD, MPH, of the Ohio State University Wexner Medical Center, Columbus, and also not part of the study, described how these inequities are magnified through bias in patient selection.

"Often times two very similar patients may present with the same medical profile and social circumstances; however, one is turned down," she said. "Often the patient turned down is the non-Hispanic Black patient while the non-Hispanic White patient is given a pass."

Dr. Conteh suggested that the first step in fixing this bias is recognizing that it is a problem and calling it by its proper name.

"As transplant centers, in order to address and change these significant disparities, we must first be willing to acknowledge that they do exist," she said. "Only then can we move to the next step of developing awareness and methods to actively combat what we should label as systemic discrimination in medicine. Transplantation is a lifesaving treatment for many patients with decompensated liver disease or liver cancer. Ensuring equitable access for all patients and populations is of paramount importance."

"Inequities such as these are unacceptable, given our mandate to distribute organs in a fair and equitable fashion."

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.

The study was supported by a Health Resources and Services Administration contract, as well as grants from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases. The investigators and interviewees reported no conflicts of interest.

ginews@gastro.org

Pediatric NAFLD almost always stems from excess body weight

BY WILL PASS

Nonalcoholic fatty liver disease in children is almost always caused by excess body weight, not other etiologies, based on a retrospective analysis of 900 patients.

Just 2% of children with overweight or obesity and suspected nonalcoholic fatty liver disease (NAFLD) had other causes of liver disease, and none tested positive for autoimmune hepatitis (AIH), reported lead author Toshifumi Yodoshi, MD, PhD, of Cincinnati Children's Hospital Medical Center, and colleagues.

"Currently, recommended testing of patients with suspected NAFLD includes ruling out the following conditions: AIH, Wilson disease, hemochromatosis, alpha-1 antitrypsin [A1AT] deficiency, viral hepatitis, celiac disease, and thyroid dysfunction," the investigators wrote in Pediatrics (2021 Apr 1. doi: 10.1016/j.jcmgh.2020.12.012).

Yet evidence supporting this particular battery of tests is scant; just one previous pediatric study has estimated the prevalence of other liver diseases among children with suspected NAFLD (Aliment Pharmacol Ther. 2013 Nov;38[10]:1267-77). The study showed that the second–most common etiology, after NAFLD, was AIH, at a rate of 4%.

But "the generalizability of these findings is uncertain," noted Dr. Yodoshi and colleagues, as the study was conducted at one tertiary center in the western United States, among a population that was predominantly Hispanic.

This uncertainty spurred the present study,

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Continued from page 30

which was conducted at two pediatric centers: Cincinnati Children's Hospital Medical Center (2009-2017) and Yale New Haven (Conn.) Children's Hospital (2012-2017).

The final analysis involved 900 patients aged 18 years or younger with suspected NAFLD based on hepatic steatosis detected via imaging and/or elevated serum aminotransferases. Demographically, a slight majority of the patients were boys (63%), and approximately one-quarter (26%) were Hispanic. Median body mass index *z* score was 2.45, with three out of four patients (76%) exhibiting severe obesity. Out of 900 patients, 358 (40%) underwent liver biopsy, among whom 46% had confirmed nonalcoholic steatohepatitis.

"Linking community-based initiatives focused on adequate nutritional support with pediatric clinical support services is critical in solving issues related to overweight in children."

All patients underwent testing to exclude the aforementioned conditions using various diagnostics, revealing that just 2% of the population had etiologies other than NAFLD.

Specifically, 11 children had thyroid dysfunction (1.2%), 3 had celiac disease (0.4%), 3 had A1AT deficiency (0.4%), 1 had hemophagocytic lymphohistiocytosis, and 1 had Hodgkin's lymphoma. None of the children had Wilson disease, hepatitis B or C, or AIH.


Dr. Rushton

Dr. Yodoshi and colleagues highlighted the latter finding, noting that 13% of the patients had autoantibodies for AIH, but "none met composite criteria." This contrasts with the previous study from 2013, which found an AIH rate of 4%.

"Nonetheless," the investigators went on, "NAFLD remains a diagnosis of exclusion, and key conditions that require specific treatments must be ruled out in the workup of patients with suspected NAFLD. In the future, the cost-effectiveness of this approach will need to be investigated."

Interpreting the findings, Francis E. Rushton, MD, of Beaufort (S.C.) Memorial Hospital emphasized the implications for preventive and interventional health care.

"This study showing an absence of etiologies other than obesity in overweight children with NAFLD provides further impetus for pediatricians to work on both preventive and treatment regimens for weight issues," Dr. Rushton said. "Linking community-based initiatives focused on adequate nutritional support with pediatric clinical support services is critical in solving issues related to overweight in children. Tracking BMI over time and developing healthy habit goals for patients are key parts of clinical interventions."

The study was funded by the National Institutes of Health. The investigators reported no conflicts of interest.

ginews@gastro.org

Treatment paradigm for chronic HBV in flux

BY BRUCE JANCIN

These days deciding when to stop targeted treatment for chronic hepatitis B is a bigger challenge than knowing when to start, Norah A. Terrault, MD, MPH, observed at the Gastroenterology Updates, IBD, Liver Disease Conference.

That's because the treatment paradigm is in flux. The strategy is shifting from achieving hepatitis B virus (HBV) DNA suppression through indefinite use of nucleoside analogues to striving for functional cure, which means eliminating hepatitis B surface antigen (HBsAg) and sustained inactive chronic hepatitis B off therapy. It's a goal that recognizes that, while suppression is worthwhile because it reduces a patient's risk of hepatocellular carcinoma, HBsAg clearance is better because it's associated with an even lower risk of the malignancy, explained Dr. Terrault, professor of medicine and chief of gastroenterology and liver diseases at the University of Southern California, Los Angeles.

The current strategy in patients who are hepatitis B e antigen (HBeAg) positive at the outset is to treat with a nucleoside analogue until seroconversion, followed by a further year or more of consolidation therapy then treatment withdrawal. It's a rational approach whose primary benefit is it allows identification of the roughly 50% of patients who can remain off treatment with inactive chronic hepatitis B. The other 50% – those who experience clinical relapse – will need retreatment.

Factors predictive of increased likelihood of a sustained off-treatment response include age younger than 40 years at the time of seroconversion, more than 1 year of consolidation therapy, and undetectable HBV DNA at cessation of treatment.

"In my own practice now, I actually extend the consolidation period for 2 years before I consider stopping, and I really favor doing a trial of stopping treatment in those who are younger," Dr. Terrault said.

The biggest change in thinking involves the duration of therapy in patients who are HBeAg negative. The strategy has been to treat indefinitely unless there is a compelling reason to stop, such as toxicity, cost, or patient preference. However, it has now been demonstrated in at least nine published studies that withdrawal of therapy has a favorable immunologic effect in noncirrhotic patients with HBeAg-negative chronic hepatitis B who have been HBV DNA negative on nucleoside analogues for at least 3 years. This trial off therapy can bring major benefits because roughly 50% of patients will have sustained inactive chronic hepatitis B off-treatment and 20% of patients will become HbsAg negative with functional cure at 3-5 years of follow-up.

"This is what's impressive: that 20% of patients have lost surface antigen, because if you continue HbeAg-negative patients on nucleoside analogue therapy, essentially none of them lose surface antigen. This is an impressive number, and you're also able to identify about 50% of patients who didn't need to be on treatment because they now have immune control and can remain inactive carriers off treatment," the gastroenterologist commented.

Treatment withdrawal in HBeAg-negative patients usually is followed by disease flares 8-12 weeks later because of host immune clearance, and therein lies a problem.

"The challenge with the withdrawal strategy is these flares that appear to be necessary and important, can be good or bad, and we're really not very good at predicting what the flare is going to look like and how severe it's going to be," according to Dr. Terrault, first author of the current American Association for the Study of Liver Diseases guidance on prevention, diagnosis, and treatment of chronic hepatitis B (Hepatology. 2018 Apr;67[4]:1560-99).

TETRA IMAGES/GETTY IMAGES

The good flares are accompanied by a reductions in HBV DNA and viral proteins, loss of HbsAg, and preserved liver function. The bad flares entail excessive host immune clearance leading to liver dysfunction or failure, with no reduction in viral proteins. The search is on for predictors of response to treatment withdrawal in HbeAg-negative patients. Potential differences in outcomes with the three available nucleoside analogues are being looked at, as are duration of viral suppression on treatment and differences in patient characteristics. A low quantitative HbsAg level at the time of drug withdrawal may also be important as a predictor of a higher likelihood of HBsAg loss over time off treatment.

"The studies that have been done are basically withdrawing everyone and then seeing what happens. I think we want to have a more refined approach," she said.

This is an unfolding story. The encouraging news is that the drug development pipeline is rich with agents with a variety of mechanisms aimed at achieving HbsAg loss with finite therapy. Some of the studies are now in phase 2 and 3.

"We should be extremely excited," Dr. Terrault said. "I think in the future we're very likely to have curative therapies in a much greater proportion of our patients."

When to start nucleoside analogues

Three antiviral oral nucleoside analogues are available as preferred therapies for chronic HBV: entecavir (Baraclude), tenofovir alafenamide (Vemlidy), and tenofovir disoproxil (Viread). All three provide high antiviral efficacy and low risk for resistance. The treatment goal is to prevent disease progression and HBV complications, including hepatocellular carcinoma, in individuals with active chronic hepatitis B.

The major liver disease medical societies differ only slightly on the criteria for starting treatment. Broadly, they recommend starting therapy in all patients with cirrhosis, as well as in patients without cirrhosis who have both a serum ALT level more than twice the upper limit of normal and elevated HBV DNA levels. The treatment threshold for HBV DNA levels is higher in patients who are HBeAg positive than it is for patients who are HBeAg negative; for example, the American Association for the Study of Liver Diseases recommends that an HbeAg-positive patient should have a HBV DNA titer greater than 20,000 IU/mL, which is a level 10 times higher than the group's treatment threshold in HBeAg-negative patients. However, these thresholds are intended as guidance, not absolute rules, Dr. Terrault emphasized. Nearly 40% of patients don't meet the dual ALT and HBV DNA thresholds, and serial monitoring of such patients for 6-12 months is recommended because they may be in transition.

The choice of nucleoside analogue is largely based on comorbidities. Any of the three preferred antivirals can be used when there are none. Tenofovir disoproxil is preferred in pregnancy because of its safety profile in that setting. In patients who are aged over 60 years or have bone disease or renal impairment, tenofovir alafenamide and entecavir are preferred. Entecavir should be avoided in favor of either form of tenofovir in patients who are HIV positive or have prior exposure to lamivudine.

Regarding treatment with these drugs, the recommendations target those whose liver disease is being driven by active HBV rather than fatty liver disease or some other cause. That's the reason for the reserving treatment for patients with both high HBV DNA and high serum ALT.

"There's definitely a camp that feels these are safe drugs, easy to use, and we should treat more people. I have to say I'm not hanging out in that camp. I still feel we should do targeted treatment, especially since there are many new drugs coming where we're going to be able to offer cure to more people. So I feel like putting everybody on suppressive therapy isn't the answer," she said.

Dr. Terrault receives research grants from and/or serves as a consultant to numerous pharmaceutical companies.

bjancin@mdedge.com

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" from page 18: Hepatic portal venous gas

The CT scan of the abdomen and pelvis depicts portal venous gas throughout the liver (Figure A, B, white arrows). Hepatic portal venous gas is traditionally regarded as an ominous radiologic sign and appears as a branching area of low attenuation on CT scanning extending to within 2 cm of the liver capsule.[1] It is commonly associated with numerous underlying abdominal diseases, ranging from benign processes to potentially lethal etiologies requiring immediate surgical intervention. The mechanism of hepatic portal venous gas can involve mechanical injury to the bowel lumen or gas-producing bacteria in the intestine.[2] In the specific case of caustic ingestion of H_2O_2, the presence of bubbles in the portal vein could result from the oxygen generated by the caustic after passage through damaged gastric mucosa or from generation of oxygen in the blood after absorption of the caustic.[3]

Despite numerous reports of satisfactory outcomes with conservative management, the discovery of portal venous gas should not be dismissed quickly. Ultimately, management should be tailored to the underlying etiology and may include urgent surgical intervention. When appropriate, conservative management may include intravenous fluids and proton pump inhibitors.[2,3] However, in cases involving caustic ingestion and massive gas embolization, providers should maintain a high index of clinical suspicion for neurologic as well as cardiac complications, because these complications may benefit from hyperbaric oxygen therapy.[2]

In this case, the patient had severe symptoms. Therefore, a decision was made to treat him with intravenous fluids, proton pump inhibitors, and two rounds of hyperbaric oxygen therapy. The patient ultimately had an uneventful recovery.

The quiz authors disclose no conflicts.

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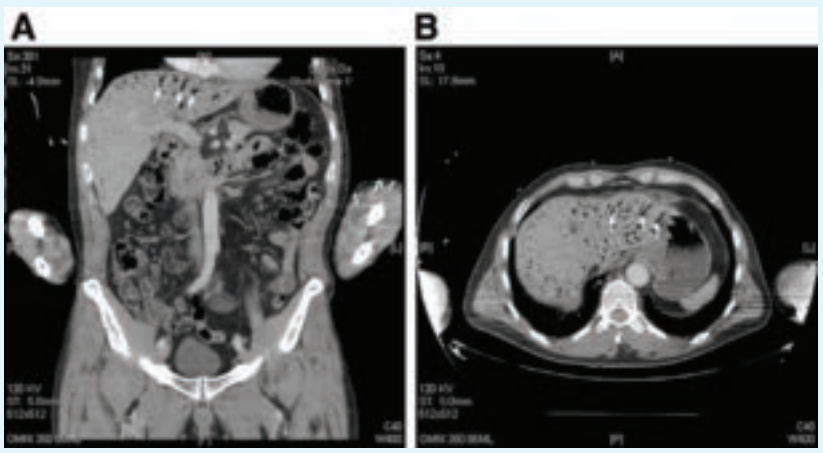

AI device approved to spot colon lesions

BY LAIRD HARRISON

The Food and Drug Administration has granted its first-ever approval of an artificial intelligence device to help find colon lesions during colonoscopy.

The GI Genius (Cosmo Artificial Intelligence) identifies areas of the colon where a colorectal polyp or tumor might be located. Clinicians then follow up with a closer examination and possible treatment.

The device does not diagnose the lesions or recommend treatments and is also not intended to take the place of laboratory sampling.

More information on the GI Genius is available on the FDA website.

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

Verification bias casts doubt on IgA tTG in celiac

BY JIM KLING

Immunoglobulin A tissue transglutaminase (IgA tTg) offers a noninvasive way to detect celiac disease, but new research suggests that its sensitivity may be overestimated and that it may not be an effective screening test, at least in asymptomatic individuals. The reason comes down to verification bias, wherein a technique appears to have higher sensitivity and lower specificity because individuals who screen positive are more likely to have their disease confirmed by a follow-up small-bowel biopsy while those who screen negative are unlikely to have a follow-up biopsy that could reveal missed celiac disease.

"The issue with verification bias is that, only the patients that screen positive on that index test are going to be getting the reference test, so there's probably a good chance that if they screen positive when they go to that reference test, they'll also be positive. What you're missing when you're calculating sensitivity is, what about the ones that are negative on the index test? Would they have been positive on that reference test? That's not even coming into your calculation because they're not getting that reference test," said Marisa Stahl, MD, a physician and researcher at the Children's Hospital Colorado Center of Celiac Disease in Aurora. Dr. Stahl was not involved in the meta-analysis, but commented on it in an interview.

The only way to fully correct for this bias is to conduct both IgA tTG testing and small-bowel biopsy on a complete or random sample of patients and compare the sensitivity and specificity of IgA tTG with the preferred method small-bowel biopsy. However, this is rarely done.

Instead, when the U.S. Preventive Services Task Force concluded that evidence was insufficient for IgA tTG testing for celiac disease, it relied on a 2016 comparative effectiveness review of nine studies that estimated sensitivity at 92.6% and specificity at 97.6% (JAMA. 2017 Mar 28;317[12]:1252-7). USPSTF remained noncommittal because of inadequate evidence surrounding the balance of benefit and harms of screening for celiac disease in asymptomatic individuals.

In the current meta-analysis, Isabel Hujoel, MD, of the Mayo Clinic, Rochester, Minn., and colleagues tested whether the studies used by USPSTF may have overestimated sensitivity because of verification bias. In a report in the Journal of Clinical Gastroenterology (2021 Apr 1;55[4]:327-34), they reviewed those same nine studies to see the potential impact of verification bias. They rated each individual study as being at high, low, or unclear risk of verification bias and found five they considered to be high risk.


Dr. Stahl

To reveal the impact of small-bowel biopsy referral rates on sensitivity and specificity, the researchers reviewed a separate set of nine retrospective and prospective studies to determine the frequency of referral for both IgA tTG–positive patients (positive referral rate) and IgA tTG–negative patients (negative referral rate), which were 79.2% and 3.6%, respectively.

The researchers then used these values to recalculate the sensitivities and specificities in the five original studies considered high risk for verification bias, then pooled those adjusted values with the remaining, unadjusted values from the studies considered low or unclear risk of bias. The new overall values were 57.1% sensitivity (95% confidence interval, 35.4%-76.4%) and 99.6% specificity (95% CI, 98.4%-99.9%).

"The reported sensitivity and specificity of IgA tTG ... are substantially biased due to a lack of adjustment for verification bias. Specifically, adjusting for verification bias decreases the sensitivity of IgA tTG from 92.5% to 57.1%, with a drop in the lower limit of the 95% CI to 35.4%, and an increase in the specificity from 97.9% to 99.6%, The low estimated sensitivity of IgA tTG raises concern on the accuracy of this test and supports performing a systematic review that accounts for verification bias. ... After adjusting for verification bias, the estimated sensitivity of IgA tTG falls to the point where the serologic marker may no longer be clinically useful as a screening test," the authors wrote.

The numbers came as a bit of a shock to Dr. Stahl because the sensitivity was so much lower than has been traditionally accepted.

"But the more important concept from the paper is that the sensitivity is probably lower than what we oftentimes reference, and we should think more about the population of patients that could potentially screen negative and still have celiac disease," she said. Although there is no literature to back this up at this time, Dr. Stahl also believes that this may be more common in adults, who have a higher incidence of seronegative Celiac disease.

The issue isn't restricted to celiac disease. Verification bias can also affect the sensitivity and specificity values from other index screens that are followed by invasive reference tests, like occult blood and colonoscopy or hepatitis C serology and liver biopsy. "A lot of times you ethically cannot put everyone through the [more invasive] reference test, so it definitely applies to other tests we screen for in GI. When we're quoting numbers and doing systematic reviews and meta-analyses, we should be accounting for those biases," said Dr. Stahl.

No source of funding was disclosed. The authors declared that they have nothing to disclose. Dr. Stahl consults for Evo-Endo.

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AGA resource

AGA offers guidance on celiac disease to help patients maintain a gluten-free diet in the AGA GI Patient Center: www.gastro.org/celiac.

Concerns raised about recurrent infections

Infliximab *from page 1*

noted, citing a study published in Cell (2020 Dec 23;183[7]:1901-12.e9).

In the current study, published in Gut (2021. doi: 10.1136/gutjnl-2021-324388), the researchers used data from the CLARITY IBD study to identify 6,935 patients with IBD aged 5 years and older seen at 92 hospitals in the United Kingdom between Sept. 22, 2020, and Dec. 23, 2020. Of these, 4,685 were treated with infliximab, and 2,250 received vedolizumab. The proportion of study participants with a positive anti–SARS-CoV-2 antibody test was the primary outcome, with secondary outcomes including proportion with positive antibodies following positive polymerase chain reaction test for SARS-CoV-2 and the magnitude of antibody reactivity.

Substantial seroprevalence differences seen

Overall, rates of symptomatic and proven SARS-CoV-2 infection and hospitalization were similar between infliximab-treated and vedolizumab-treated patients with IBD. However,

"Although the issues that are raised in this study are of concern, patients should not have clinically beneficial therapy discontinued or switched based on these results"

seroprevalence was significantly lower in the infliximab group, compared with the vedolizumab group (3.4% vs. 6.0%; $P < .0001$). In addition, infliximab and immunomodulator use were each independently associated with lower seropositivity, compared with vedolizumab (odds ratio, 0.66 for infliximab; and OR, 0.70 for immunomodulators) in a multivariate analysis.

In a sensitivity analysis, 39 of 81 infliximab-treated patients with polymerase chain reaction–confirmed COVID-19 infection seroconverted (48%), compared with 30 of 36 vedolizumab-treated patients (83%) ($P < .00044$). Infliximab-treated patients with confirmed infections also showed a lower magnitude of anti–SARS-CoV-2 reactivity, compared with vedolizumab-treated patients ($P < .0001$).

From a clinical perspective, the lower seroconversion rates and reduced levels of anti–SARS-CoV-2 antibody reactivity might increase susceptibility to recurrent COVID-19 infections in infliximab-treated IBD patients, the researchers noted. In addition, the impaired serological responses might promote chronic nasopharyngeal colonization and consequently promote the development of COVID-19 variants and drive persistent transmission, the researchers said.

The study findings were limited by several factors including lack of knowledge on the impact of attenuated immune response on infection risk, the potential for recall bias associated with patient reports, and the focus on infliximab only, the researchers pointed out. However, the key findings are likely apply to other anti-TNF monoclonal antibodies including adalimumab, certolizumab, and golimumab, they suggested.

The study was strengthened by the recruitment of a large number of patients in a narrow time frame and comprehensive collection of data on patient-reported outcomes, COVID-19 testing, and serological assay results, the researchers said. Overall, the findings support the public health value of serological testing and virus surveillance to identify suboptimal vaccine response and to consider implications for practice, they added. "If attenuated serological responses following vaccination are also observed, then modified immunization strategies will need to be designed for millions of patients worldwide," they emphasized.

Findings inform clinical practice and public health

The study is very important for many reasons, said Kim L. Isaacs, MD, PhD, AGAF, of the University of North Carolina at Chapel Hill in an interview. "It is known that there is decreased responsiveness to a number of routine vaccinations in IBD patients on immune active therapy. In terms of SARS-CoV-2, development of an immune response with infection is important in terms of severity of infection, reinfection, and possibly limiting spread of infection in this patient population," she said. "Looking at both serum seroconversion and reactivity of immune response in patients with known SARS-CoV-2 infection will help to define clinical and public health guidance, and also may be predictive as to what might happen with SARS-CoV-2 immunization based on background biologic or immunosuppressant therapy," she noted.

Dr. Isaacs said that she was not surprised by the study findings. "Anti-TNF, thiopurine, and methotrexate therapy are all thought to be systemically active and likely to suppress the immune response to infection and vaccination," she said. Vedolizumab, on the other hand, is thought to be less systemically active and clinically is associated with fewer serious infections.

Data will drive patient counseling

"These results affect counseling of IBD patients on immune active therapy who have had a SARS-CoV-2 infection," said Dr. Isaacs. "They should be made aware that infection does not indicate protection from further infection. Although the issues that are raised in this study are of concern, patients should not have clinically beneficial therapy discontinued or switched based on these results," she said.

"Additional research is needed to determine what the seroconversion rate is with the currently available immunizations for SARS-CoV-2," said Dr. Isaacs. More questions to address include whether there are differences in the different products available, whether immunization after SARS-CoV-2 infection improves both seroconversion and immune reactivity, and whether there is any benefit to transiently stopping dual immune active therapy during the time of immunization, she said.

Further studies can fill knowledge gaps

"There is a knowledge gap in our understanding of susceptibility to SARS-CoV-2 infections among patients with IBD who have previously been infected," Shirley Cohen-Mekelburg, MD, MS, staff physician and research scientist in the inflammatory bowel disease program at the Veterans Affairs Ann Arbor (Mich.) Healthcare System, said in an interview. "This is a first step in beginning to narrow this gap – to provide patients and providers with data to drive recommendations during this COVID-19 pandemic."

Dr. Kim L. Isaacs

She added that, while further work needs to be done, the study findings do support potential benefit for ongoing vigilance among patients receiving infliximab for IBD. "The study findings also drive us to seek answers to more questions: For example, should we consider serological testing for patients on infliximab? How does the presence or absence of anti–SARS-CoV-2 antibodies associate with susceptibility to infection for patients with infliximab?

"Further studies examining anti–SARS-CoV-2 reactivity are necessary to better understand antibody responses between patients with IBD to the general population, or between patients on immunosuppressive therapy and the general population," she said. "Observational studies are also not designed to examine the causal relationship between infections, medications, and antibody responses. There may be some inherent differences to patients who receive infliximab as compared to vedolizumab for IBD."

The study was supported by Biogen (Switzerland), Celltrion Healthcare, Galapagos, F. Hoffmann–La Roche, Hull University Teaching Hospital NHS Trust, and the Royal Devon and Exeter NHS Foundation Trust. The study authors disclosed financial and nonfinancial relationships with numerous companies, including AbbVie, Biogen, Celltrion Healthcare, Galapagos, F. Hoffmann–La Roche, and Immundiagnostik, as well as Janssen, who markets infliximab, and Takeda, who markets vedolizumab. Dr. Isaacs and Dr. Cohen-Mekelburg had no relevant financial conflicts to disclose.

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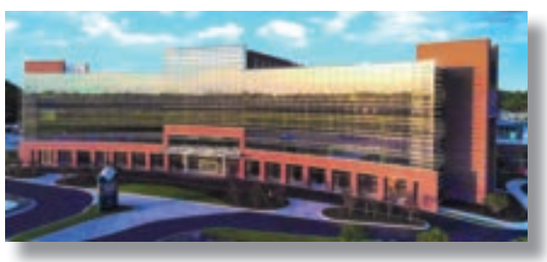

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Cumulative inflammatory burden predicts cancer risk in ulcerative colitis

BY BRUCE JANCIN

The cumulative burden of histologic inflammation is a strong predictor of colorectal neoplasia risk in ulcerative colitis, according to a recent case-control study.

David T. Rubin, MD, AGAF, was the senior author of the study, which provided independent validation of a metric for cumulative burden of inflammation as a risk stratification tool in ulcerative colitis and presented these findings at the Gastroenterology Updates, IBD, Liver Disease Conference. The metric was developed at St. Mark's Hospital, London, which he called "a leader in the field."

"The implication of demonstrating this is that, if you control inflammation and keep it controlled over time, it would imply that you can reduce the overall risk for cancer and dysplasia," explained Dr. Rubin, professor of medicine and chief of the section of gastroenterology, hepatology, and nutrition at the University of Chicago.

The original retrospective St. Mark's study included 987 patients with extensive ulcerative colitis followed with colonoscopic surveillance for a median of 13 years. Each colonoscopy was scored for severity of microscopic inflammation on a 0-3 scale. The investigators calculated a patient's cumulative inflammatory burden by adding each histologic inflammatory activity score and multiplying that figure by the surveillance interval in years.

In a multivariate analysis, the London investigators demonstrated that the risk of colorectal neoplasia jumped by 2.1-fold for each 10-unit increase in cumulative inflammatory burden, defined as the equivalent of either 10 years of continuous mild active histologic inflammation, 5 years of continuous moderate inflammation, or 3.3 years of continuous severe inflammation (Gut. 2019 Mar;68[3]:414-22).

The University of Chicago retrospective external validation study included 26 ulcerative colitis patients with colorectal neoplasia and 36 others without cancer (Inflamm Bowel Dis. 2021 Jan 19;27[2]:203-6). The mean cumulative histologic inflammatory activity score in the group with colorectal neoplasia was 12.63, compared with 7.98 in controls. For each 1-unit increase in cumulative inflammatory burden the risk of developing colorectal neoplasia increased by 8%, consistent with the magnitude of the hazard previously reported at St. Mark's.

"The way you could take this back to your practice is by thinking carefully about what is the degree of inflammation each time you've done a colonoscopy and considering whether the patient who is in deep remission and doing well might deserve a longer interval between their next exam and the one you just completed," according to the gastroenterologist.

"The most interval I give a patient is 3 years – for somebody in deep remission with no inflammation on the last exam. And when they've had prior inflammation but are now doing well, I keep in mind what that prior inflammation was. We're now working on using that cumulative histologic inflammation score to guide intervals, but we don't have

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Can smoke exposure inform CRC surveillance in IBD?

BY JIM KLING

FROM THE CROHN'S AND COLITIS CONGRESS

Cigarette smoking may be associated with a higher probability of developing colorectal neoplasia (CRN) among patients with inflammatory bowel disease (IBD), a finding that if confirmed could help to refine colorectal cancer surveillance guidelines. IBD patients undergo surveillance at specific time points of their disease with the aim to detect and potentially treat early CRN.

But these procedures are costly and burdensome to patients, and some previous studies have revealed a relatively low utility for patients, according to Kimberley van der Sloot, MD, a PhD candidate at the University Medical Center Groningen (the Netherlands). She presented the research at the annual congress of the Crohn's & Colitis Foundation and the American Gastroenterological Association. The study was also published in Clinical Gastroenterology and Hepatology (2021 Jan 13. doi: 10.1016/j.cgh.2021.01.015).

"We aimed to explore the role of cigarette exposure in colorectal neoplasia risk in patients with IBD, and we aimed to improve the CRN risk stratification model that we are currently using for these surveillance guidelines," Dr. van der Sloot said during her talk.

Commenters during the Q&A period noted that the population database used in the study did not include measures of inflammation, which is a known risk for CRN. One review found that smoking worsens inflammation in Crohn's disease but improves it in ulcerative colitis (Best Pract Res Clin Gastroenterol. 2004 Jun;18[3]:481-96).

"It certainly raises the issue that we've always said, which is that people should quit smoking for other health reasons, but it doesn't necessarily answer the question definitively," said David T. Rubin, MD, AGAF, who moderated the session and is professor of medicine at the University of Chicago and chair of the congress's organizing committee. He added that the association between smoking and CRN risk may nevertheless inform future management surveillance guidelines if it is confirmed.

The researchers analyzed data from the 1000IBD cohort, which is prospectively following IBD patients in the Netherlands. The study included 1,386 patients who had at least one colorectal biopsy. Compared to a general population CRN incidence of 2.4%, Crohn's disease patients who were never smokers had an incidence of 4.7% versus 10.3% among former or current smokers. In ulcerative colitis, the incidence was 12.5% among never smokers and 17.9% among former or current smokers.

Dr. Kimberley van der Sloot

TERROA/GETTY IMAGES

In Crohn's disease, previous or current smokers had about a twofold increased risk (hazard ratio, 2.04; $P = .044$). Compared to never smokers, former smokers trended toward an increased risk (HR, 2.16; $P = .051$), and active smokers had a significantly increased risk (HR, 2.20; $P = .044$). Passive smoke exposure was also associated with greater risk, both in childhood (HR, 4.79; $P = .003$) and current (HR, 1.87; $P = .024$).

In ulcerative colitis, the only statistically significant association between smoke exposure and CRN risk was among former smokers (HR, 1.73; $P = .032$).

The researchers also looked at patients with a disease duration longer than 8 years and stratified patients according to low risk (left-side ulcerative colitis, <50% of colon affected in Crohn's disease; n = 425), medium risk (postinflammatory polyposis present or extensive colitis; n = 467), and high risk (concordant primary sclerosing cholangitis or having a first-degree relative with colorectal cancer; n = 143). In Crohn's disease, current smoking was associated with greater CRN incidence ($P = .046$), and former smoking trended in that direction but was nonsignificant ($P = .068$). Former smoking also trended toward a risk in ulcerative colitis ($P = .068$), but there was no sign of an association for current smoking ($P = .883$).

In Crohn's disease, after adjustment for risk stratification, greater CRN risk was associated with passive smoke exposure both during childhood ($P = .001$) and at present ($P = .003$).

"We believe this is the first study to describe the important role of cigarette smoking in development of colorectal neoplasia in IBD patients in a large, prospective, cohort, and I think [it] has shown the importance of lifestyle and smoking particularly in IBD. This is one more example. Alongside that, we've shown that adding this risk factor can improve the current risk stratification that is used for surveillance guidelines, and might be of benefit in the development of future guidelines," said Dr. van der Sloot.

Dr. van der Sloot and Dr. Rubin had no relevant financial disclosures.

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prospective data to validate this approach. So when you're not sure, the conservative approach is surveillance colonoscopy every 1-2 years after you've had 10 years of disease. That's probably overutilization of our resources, but we don't have a better way to do it yet," Dr. Rubin said.

The novel metric for calculating cumulative histologic inflammation burden as a means of predicting colorectal cancer in ulcerative colitis dovetails with the current emphasis upon individualized risk assessment as recommended in the latest American College of Gastroenterology practice guidelines, for which Dr. Rubin was first author (Am J Gastroenterol. 2019 Mar;114[3]:384-413).

"Like we individualize our treatments, we should individualize our colorectal cancer screening and prevention strategies," he emphasized.

Risk factors for colorectal cancer and dysplasia in patients with ulcerative colitis can be grouped as either potentially modifiable or immutable. Potentially modifiable risk factors include backwash ileitis, pseudopolyps, prior dysplasia, and mass or stricture, as well as the degree of histologic inflammation. Immutable risk factors include younger age at diagnosis, male gender, duration and extent of disease, family history of colorectal cancer, and primary sclerosing cholangitis, Dr. Rubin noted.

He reported receiving grant support from and/or serving as a consultant to more than two dozen medical companies.

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