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University of Oxford

Dr. Dimitrios A. Koutoukidis and colleagues found in a meta-analysis that structured weight loss programs improved liver biomarkers in NAFLD.

Formal weight loss programs improve NAFLD

BY WILL PASS
MDedge News

For patients with nonalcoholic fatty liver disease (NAFLD), formal weight loss programs lead to statistically and clinically significant improvements in biomarkers of liver disease, based on a recent meta-analysis.

The findings support changing NAFLD guidelines to recommend weight loss interventions, according to lead author Dimitrios A. Koutoukidis, PhD, of the University of Oxford (England) and colleagues.

"Clinical guidelines around the world recommend physicians offer advice on lifestyle modification, which mostly includes weight loss through hypoenergetic diets and increased physical activity," the investigators wrote in JAMA Internal Medicine. "However, ... guidelines rarely specifically recommend treatment programs to support weight loss," they added.

To investigate associations between methods of weight loss and improvements in NAFLD, the investigators screened for studies involv-

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Appeals court may strike down ACA

The individual mandate is the crux.

BY ALICIA GALLEGOS
MDedge News

Appellate judges appeared to doubt that the Affordable Care Act should survive without the law's signature insurance mandate during oral arguments on July 9, in a highly watched legal battle that may upend the health care law.

During the 2-hour hearing, a three-judge panel for the 5th U.S. Circuit Court of Appeals peppered attorneys with questions about whether Congress intended the ACA to function without the individual mandate, and the panel seemed doubtful the law can stand if the regulation is parsed, according to an audio transcript of the arguments. As written, the individual mandate required that all Americans have insurance or pay a tax penalty. However, budget legislation in 2017 zeroed out the penalties associated with the mandate, rendering it unenforceable.

Appeals Judge Kurt Engelhardt, a President Trump appointee, asked defense attorney Samuel Siegel why Congress failed to add a clause in the original law that would have

See **Court** · *page 22*

INSIDE

AGA remembers Dr. Henry T. Lynch

Henry T. Lynch, MD, came from a humble background, growing up in a rough neighborhood in New York City. He enlisted in the Navy and served in the South Pacific during World War II. Afterward, Dr. Lynch focused his efforts on completing his education, which eventually lead him to the medical field.

After obtaining his high-school equivalency, and completing his undergraduate degree at the University of Oklahoma and his master's degree in clinical psychology at the University of Denver, his path turned toward the field in which he would make his thrilling and unprecedented discoveries. He studied for a PhD in human genetics at the University of Texas at Austin and received his medical degree from the University of Texas Medical Branch in Galveston. He completed his internship at St. Mary's Hospital in Evansville, Indi-

See **Dr. Lynch** · *page 12*

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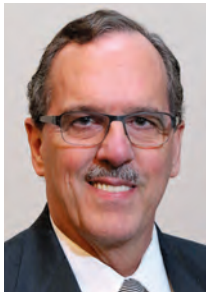
LETTER FROM THE EDITOR: *We owe a lot to scientists like Dr. Henry T. Lynch*

It is with great sadness that we note the passing (June 2, 2019; age 91) of Henry T. Lynch, MD. Dr. Lynch almost singlehandedly brought attention to the genetic syndrome that bears his name. In 1913 Aldred Warthin (pathology chair at the University of Michigan) first described family "G", the family of his seamstress who had told him that her family all dies of cancer. She herself succumbed to endometrial cancer. A plaque commemorating Dr. Warthin hangs down the hallway from my office at Michigan. His report fell into obscurity until the 1960s when Dr. Lynch arranged a reunion of family G in Ann Arbor, leading to a detailed update of the family in 1971. He recognized the autosomal dominance of the pedigree pattern.

In 1973, C. Richard Boland, MD (past AGA President), wrote a medical school thesis entitled "A Familial Cancer Syndrome" and subsequently published two papers in which he first used the term "Lynch syndrome (I and II)." Dr. Boland (whose family also carried a Lynch syndrome variant) spent his career adding to our molecular and clinical knowledge about nonpolyposis colon cancer syndromes. In the 1990s Vogelstein and others first described the molecular pathways that lead to colon cancer – and the rest is history.

I was a young faculty gastroenterologist at the Minneapolis VA Medical Center when one day my phone rang; it was Henry Lynch. He wanted to alert me that one of his patients was coming to me for surveillance colonoscopy. He explained the importance of what I was to do and how I should follow this man. I was overwhelmed by his attention to his patient (one of thousands) and his kindness to me. I had the privilege of traveling with him as visiting professors on a trip to South America. He was one of the kindest, most intelligent, and gracious persons I had ever met. I never forgot that experience.


Dr. Allen

We owe a lot to scientists, clinicians, and thought leaders like Henry Lynch who provide us the scientific basis of the care we give our patients.

We owe a lot to scientists, clinicians, and thought leaders like Henry Lynch who provide us the scientific basis of the care we give our patients.

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

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz

Q1. A 21-year-old woman is diagnosed with autoimmune hepatitis and is started on prednisone and azathioprine. Within a week, she develops mid-abdominal pain, radiating to the back, and her lipase level is 537 U/L.

What alternative therapy may be useful in this patient?
A. Cyclophosphamide
B. Anakinra
C. Mycophenelate mofetil
D. Infliximab
E. Natalizumab

Q2. Which of the following statements regarding the sensitivity of a radiologic study to detect active bleeding in the GI tract is most accurate?
A. Bleeding must exceed 0.5 cc/min to be detected with tagged red blood cell scintigraphy.
B. A positive tagged red blood cell scintigraphy study accurately shows the location of the bleeding 90% or more of the time.
C. A bleeding protocol CT scan can detect bleeding at rates as low as 0.1 cc/min.
D. Angiography is more useful in patients with normal blood pressure and low transfusion demands.
E. Angiography detects bleeding at rates of 0.5-1 cc/min.

The answers are on page 13.

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Editorial Offices 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548
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Underwater EMR may be option for colorectal lesions

BY WILL PASS
MDedge News

For intermediate-size colorectal lesions, underwater endoscopic mucosal resection (UEMR) may offer cleaner margins than conventional EMR without increasing procedure time or risk of adverse events, based on a recent head-to-head trial conducted in Japan.

UEMR was associated with higher R0 and en bloc resection rates than was conventional EMR (CEMR) when used for intermediate-size colorectal lesions, reported lead author Takeshi Yamashina, MD, of Osaka (Japan) International Cancer Institute, and colleagues. The study was the first multicenter, randomized trial to demonstrate the superiority of UEMR over CEMR, they noted.

Although CEMR is a well-established method of removing sessile colorectal lesions, those larger than 10 mm can be difficult to resect en bloc, which contributes to a local recurrence rate exceeding 15% when alternative, piecemeal resection is performed, the investigators explained in Gastroenterology.

Recently, UEMR has emerged as "an alternative to CEMR and is reported to be effective for removing flat or large colorectal polyps," the investigators wrote. "With UEMR, the bowel lumen is filled with water instead of air/CO_2, and the lesion is captured and resected with a snare without submucosal injection of normal saline."

To find out if UEMR offers better results than CEMR, the investigators recruited 211 patients with 214 colorectal lesions at five centers in Japan. Patients were aged at least 20 years and had mucosal lesions of 10-20 mm in diameter. Based on macroscopic appearance, pit pattern classification with magnifying chromoendoscopy, or narrow-band imaging, lesions were classified as adenoma, sessile serrated adenoma/polyp, or intramucosal adenocarcinoma. Patients were randomly assigned in a 1:1 ratio to the UEMR or CEMR group, and just prior to the procedure, operators were informed of the allocated treatment. Ten expert operators were involved, each with at least 10 years of experience, in addition to 18 nonexpert operators with less than 10 years of experience. The primary endpoint was the difference in R0 resection rate between the two groups, with R0 defined as en bloc resection with histologically negative margins. Secondary endpoints were en bloc resection rate, adverse events, and procedure time.

The results showed a clear win for UEMR, with an R0 rate of 69%, compared with 50% for CEMR (P = .011), and an en bloc resection rate that followed the same trend (89% vs. 75%; P = .007). Neither median procedure times nor number of adverse events were significantly

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Genomic study reveals five subtypes of colorectal cancer

BY WILL PASS
MDedge News

Colorectal cancer can be divided into five DNA methylation subtypes that predict molecular and clinical behavior and may offer future therapeutic targets, according to investigators.

In 216 unselected colorectal cancers, five subtypes of the CpG island methylator phenotype (CIMP) showed "striking" associations with sex, age, and tumor location, reported lead author Lochlan Fennell, MD, of the QIMR Berghofer Medical Research Institute in Queensland, Australia, and colleagues. CIMP level increased with age in a stepwise fashion, they noted.

Further associations with CIMP subtype and BRAF mutation status support the investigators' recent report that sessile serrated adenomas are rare in young patients and pose little risk of malignancy. With additional research, these findings could "inform the development of patient-centric surveillance for young and older patients who present with sessile serrated adenomas," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology.

"CIMP can be detected using a standardized marker panel to stratify tumors as CIMP-high, CIMP-low, or CIMP-negative." In the present study, the investigators expanded these three existing subtypes into five subtypes, allowing for better prediction of clinical and molecular characteristics associated with disease progression.

Initial genomic testing showed that 13.4% of cases carried a BRAF V600E mutation, 34.7% were mutated at KRAS codon 12 or 13, and almost half of the patients (42.2%) had a TP53 mutation. Sorted into the three previously described subtypes, CIMP negative was most common (68.5%), followed by CIMP low (20.4%), and CIMP high (11.1%). About two-thirds (66%) of BRAF mutant cancers were CIMP high, compared with just 3% of BRAF wild-type cases (*P* less than .0001). KRAS mutated cases were more often CIMP-low than KRAS wild-type cancers (34.6% vs. 12.8%; *P* less than .001).

With use of Illumina HumanMethylation450 Bead Chip arrays and recursively partitioned mixed model clustering, five methylation clusters were identified; specifically, these were CIMP-H1 and CIMP-H2 (high methylation levels), CIMP-L1 and CIMP-L2 (intermediate methylation levels), and CIMP-negative (low methylation level). As described above, methylation level demonstrated a direct relationship with age, ranging from CIMP-negative (61.9 years) to CIMP-H1 (75.2 years). The investigators also reported unique characteristics of each new subtype. For instance, the CIMP-H1 cluster had many features in common with cases of serrated neoplasia, such as BRAF mutation positivity (73.9%; *P* less than .0001).

"BRAF mutations are a hallmark of the serrated neoplasia pathway, and indicate that these cancers probably arose in serrated precursor lesions," the investigators wrote. "We previously showed that the colonoscopic incidence of sessile serrated adenomas does not differ between patients aged in their 30s and patients who are much older, whereas BRAF mutant cancers were restricted to older individuals, suggesting these BRAF mutant polyps may have limited malignant potential in young patients."

In contrast with the CIMP-H1 cases, CIMP-H2 cancers were more often KRAS mutant (54.5% vs. 17.4%). Other findings revealed associations with subtype and location; for example, CIMP-L1 cases were located equally in the distal and proximal colon, whereas CIMP-L2 cases more often localized to the distal colon and rectum. Of note for CIMP-negative cancers, most (62.3%) occurred in the distal colon, and none had a BRAF mutation.

The five methylation subtypes also showed associations with consensus molecular subtypes (CMS) to varying degrees. The two strongest correlations were found in CIMP-H1 cancers and CIMP-H2 cancers, which were most frequently classified as CMS1 (69.6%) and CMS3 (54.5%), respectively.

Continued on following page

Genomic, epigenomic, and transcriptomic information has revealed molecular subclasses of colorectal cancer (CRC), which has refined our understanding of the molecular and cellular biology of CRC and improved our treatment of patients with CRC. Several reliable and clinically useful molecular subtypes of colorectal cancer have been identified, including microsatellite unstable (MSI), chromosomal unstable (CIN), CIMP, and CMS 1-4 subtypes. Despite these substantial advances, it is also clear that we still only partially grasp the molecular and cellular biology driving CRC.


Dr. Grady

The studies by Fennell et al. provide new insights into the CIMP subtype of CRC that address this knowledge gap. Using a large CRC cohort and more detailed molecular information than available in prior studies, they have identified previously unrecognized CRC CIMP subtypes that have unique methylomes and mutation patterns. These five CIMP subclasses vary with regard to location in the colon, and frequency of mutations in KRAS, BRAF, and MSI, as well as alterations in epigenetic regulatory genes. The observations related to differences in frequencies of MSI, and mutations in KRAS and BRAF help demystify the heterogeneity in clinical and cellular behavior that has been seen in the broader class of CIMP cancers. Perhaps most importantly, their studies identify plausible driver molecular alterations unique to the CIMP subclasses, such as subclass-specific mutations in epigenetic regulatory genes and activated oncogenes. These are promising novel targets for chemoprevention strategies and therapies. Fennell and colleagues have now set the stage for functional studies of these molecular alterations to determine their true role in the cellular and clinical behavior of CRC.

William M. Grady, MD, AGAF, is the Rodger C. Haggitt Professor of Medicine, department of medicine, division of gastroenterology, University of Washington and the clinical research division, Fred Hutchinson Cancer Research Center, both in Seattle. He is an advisory board member for Freenome and SEngine; has consulted for DiaCarta, Boehringer Ingelheim, and Guardant Health; and has conducted industry-sponsored research for Janssen and Cambridge Epigenetic.

Continued from previous page

different between groups.

Subset analysis showed that UEMR was best suited for lesions at least 15 mm in diameter, although the investigators pointed out the superior R0 resection rate with UEMR held steady regardless of lesion morphology, size, location, or operator experience level.

The investigators suggested that the findings give reason to amend some existing recommendations. "Although the European Society of Gastrointestinal Endoscopy Clinical Guidelines suggest hot-snare polypectomy with submucosal injection for removing sessile polyps 10-19 mm in size, we found that UEMR was more effective than CEMR in terms of better R0 and en bloc resection rates," they wrote. "Hence, we think that UEMR will become an alternative to CEMR. It could fill the gap for removing polyps 9 mm [or larger] (indication for removal by cold-snare polypectomy) and [smaller than] 20 mm (indication for ESD removal)."

The investigators explained that UEMR achieves better outcomes primarily by improving access to lesions. Water immersion causes lesions to float upright into the lumen, while keeping the muscularis propria circular behind the submucosa, which allows for easier snaring and decreases risk of perforation. Furthermore, the investigators noted, water immersion limits flexure angulation, luminal distension, and loop formation, all of which improve maneuverability and visibility.

The investigators reported no external funding or conflicts of interest.

ginews@gastro.org

SOURCE: Yamashina T et al. Gastro. 2018 Apr 11. doi: 10.1053/j.gastro.2019.04.005.

HCC surveillance after anti-HCV therapy cost effective only for patients with cirrhosis

BY WILL PASS
MDedge News

For patients with hepatitis C virus (HCV)–related cirrhosis (F4), but not those with advanced fibrosis (F3), hepatocellular carcinoma (HCC) surveillance after a sustained virologic response (SVR) is cost effective, according to investigators.

Current international guidelines call for HCC surveillance among all patients with advanced fibrosis (F3) or cirrhosis (F4) who have achieved SVR, but this is "very unlikely to be cost effective," reported lead author Hooman Farhang Zangneh, MD, of Toronto General Hospital and colleagues. "HCV-related HCC rarely occurs in patients without cirrhosis," the investigators explained in Clinical Gastroenterology and Hepatology. "With cirrhosis present, HCC incidence is 1.4%-4.9% per year. If found early, options for curative therapy include radiofrequency ablation (RFA), surgical resection, and liver transplantation."

The investigators developed a Markov model to determine which at-risk patients could undergo surveillance while remaining below willingness-to-pay thresholds. Specifically, cost-effectiveness was assessed for ultrasound screenings annually (every year) or biannually (twice a year) among patients with advanced fibrosis (F3) or compensated cirrhosis (F4) who were aged 50 years and had an SVR.

Relevant data were drawn from expert opinions, medical literature, and Canada Life Tables. Various HCC incidence rates were tested, including a constant annual rate, rates based on type of antiviral treatment, others based on stage of fibrosis, and another that increased with age. The model was validated by applying it to patients with F3 or F4 fibrosis who had not yet achieved an SVR. All monetary values were reported in 2015 Canadian dollars.

Representative of current guidelines, the investigators first tested costs when conducting surveillance among all patients with F3 or F4 fibrosis with an assumed constant HCC annual incidence rate of 0.5%. Biannual ultrasound surveillance after SVR caught more cases of HCC still in a curable stage (78%) than no surveillance (29%); however, false-positives were relatively common at 21.8% and 15.7% for biannual and annual surveillance, respectively.

The investigators noted that, in the real world, some of these false-positive results are not detected by more advanced imaging, so patients go on to receive unnecessary RFA, which incurs additional costs. For this reason, while biannual surveillance was more effective, it was also more expensive, with an incremental cost-effectiveness ratio (ICER) of $106,792 per quality-adjusted life-years (QALY), compared with $72,105 per QALY for annual surveillance.

Including only patients with F3 fibrosis after interferon-based therapy, using an HCC incidence of 0.23%, biannual and annual ICERs rose to $484,160 and $204,708 per QALY, respectively, both of which exceed standard willingness-to-pay thresholds. In comparison, annual and biannual ICERs were at most $55,850 and $42,305 per QALY, respectively, among patients with cirrhosis before interferon-induced SVR, using an HCC incidence rate of up to 1.39% per year.

'Our analysis suggests that HCC surveillance is very unlikely to be cost effective in patients with F3 fibrosis, whereas both annual and biannual modalities are likely to be cost effective at standard willingness-to-pay thresholds for patients with cirrhosis.'

"These results suggest that biannual (or annual) HCC surveillance is likely to be cost effective for patients with cirrhosis, but not for patients with F3 fibrosis before SVR," the investigators wrote.

Costs for HCC surveillance among cirrhosis patients after direct-acting antiviral-induced SVR were still lower, at $43,229 and $34,307 per QALY, which were far lower than costs for patients with F3 fibrosis, which were $188,157 and $111,667 per QALY.

Focusing on the evident savings associated with surveillance of patients with cirrhosis, the investigators tested two diagnostic thresholds within this population with the aim of reducing costs further. They found that surveillance of patients with a pretreatment aspartate aminotransferase to platelet ratio index (APRI) greater than 2.0 (HCC incidence, 0.89%) was associated with biannual and annual ICERs of $48,729 and $37,806 per QALY, respectively, but when APRI was less than 2.0 (HCC incidence, 0.093%), surveillance was less effective and more expensive than no surveillance at all. A similar trend was found for an FIB-4 threshold of 3.25.

Employment of age-stratified risk of HCC also reduced costs of screening for patients with cirrhosis. With this strategy, ICER was $48,432 per QALY for biannual surveillance and $37,201 per QALY for annual surveillance.

"Our analysis suggests that HCC surveillance is very unlikely to be cost effective in patients with F3 fibrosis, whereas both annual and biannual modalities are likely to be cost effective at standard willingness-to-pay thresholds for patients with cirrhosis compared with no surveillance," the investigators wrote.

"Additional long-term follow-up data are required to help identify patients at highest risk of HCC after SVR to tailor surveillance guidelines," the investigators concluded.

The study was funded by the Toronto Centre for Liver Disease. The investigators declared no conflicts of interest.

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SOURCE: Zangneh HF et al. Clin Gastroenterol Hepatol. 2018 Dec 20. doi: 10.1016/j.cgh.2018.12.018.

Continued from previous page

Using CIBERSORT, the investigators detected a variety of associations between the five subtypes and stromal immune cell composition. For example, CIMP-H1 cases were enriched for macrophages, compared with the other subtypes, except CIMP-L2. Mast cells showed a stepwise relationship with subtype; they contributed the most to the immune microenvironment of CIMP-negative cancers and the least to cases classified as CIMP-H1. A converse trend was found with natural killer cells.

Of note, in CIMP-H1 and CIMP-H2 cancers, oncogenes were significantly more likely than tumor-suppressor genes to undergo gene body methylation, which is positively correlated with gene expression, and oncogenes in these subtypes had significantly greater gene body methylation than normal colonic mucosa.

"The five subtypes identified in this study are highly correlated with key clinical and molecular features, including patient age, tumor location, microsatellite instability, and oncogenic mitogen-activated protein kinase mutations," they wrote. "We show that cancers with high DNA methylation show an increased preponderance for mutating genes involved in epigenetic regulation, and namely those that are implicated in the chromatin remodeling process."

Concluding, the investigators explained the role of their research in future therapy development. "Our analyses have identified potentially druggable vulnerabilities in cancers of different methylation subtypes," they wrote. "Inhibitors targeting synthetic lethalities, such as SWI/SNF component inhibitors for those with ARID mutations, should be evaluated because these agents may be clinically beneficial to certain patient subsets."

The study was funded by the National Health and Medical Research Council, the U.S. National Institutes of Health, Pathology Queensland, and others. The investigators disclosed no conflicts of interest.

ginews@gastro.org

SOURCE: Fennell L et al. CMGH. 2019 Apr 4. doi: 10.1016/j.jcmgh.2019.04.002.

Combo therapy with anti-TNFs and immune modulators benefits Crohn's, but not UC

BY WILL PASS
MDedge News

Adding an immune modulator (IM) to anti–tumor necrosis factor (anti-TNF) initiation therapy benefits patients with Crohn's disease (CD) but not those with ulcerative colitis (UC), according to a recent retrospective look at more than 1,000 cases.

The study showed that patients with CD who started combination therapy instead of monotherapy had lower rates of treatment ineffectiveness, experienced longer delays until hospitalization, and less often needed to switch their anti-TNF agent, reported lead author Laura E. Targownik, MD, of the University of Manitoba, in Winnipeg, and colleagues.

Key clinical point
For patients with Crohn's disease, combination therapy with an immune modulator and an anti-TNF agent decreased risk of ineffectiveness by 38%, compared with anti-TNF therapy alone.

"Current guidelines on the medical management of IBD strongly support the use of IMs and anti-TNFs in combination over anti-TNF monotherapy," the investigators wrote in Clinical Gastroenterology and Hepatology. "However, there is a sparsity of real-world data demonstrating the incremental benefits of combination therapy."

The investigators noted that the SONIC trial, conducted in 2010, showed that patients treated with combination therapy were more likely to achieve corticosteroid-free remission at weeks 26 and 50; this became the basis of evidence leading multiple clinical guidelines to recommend combination therapy for patients with CD.

Results showed that patients with CD had higher rates of ineffectiveness-free survival when treated with combination therapy instead of monotherapy at 1 year (74.2% vs. 68.6%) and 2 years (64.0% vs. 54.5%). Choice of agent from either class had no influence on effectiveness of combination therapy.

The present study involved 852 patients with CD and 303 with UC who began treatment with an anti-TNF agent during 2001-2016. Data were drawn from the Manitoba Inflammatory Bowel Disease Epidemiology database.

The main outcome of interest was treatment ineffectiveness, which was defined by any of the following four events: acute, IBD-related hospital admission for more than 48 hours; resective intestinal surgery; corticosteroid use at least 14 days after initiating anti-TNF therapy, or, if corticosteroids were used within 16 weeks of anti-TNF initiation, then subsequent corticosteroid use occurring at least 16 weeks after initiation; or switching to a different anti-TNF agent. The investigators also looked for differences in effectiveness between two agents from each class: anti-TNF agents infliximab and adalimumab, and immunomodulators methotrexate and azathioprine.

Results showed that patients with CD had higher rates of ineffectiveness-free survival when treated with combination therapy instead of monotherapy at 1 year (74.2% vs. 68.6%) and 2 years (64.0% vs. 54.5%). With a Cox proportional hazards model, this translated to a 38% reduced risk of treatment ineffectiveness (adjusted hazard ratio, 0.62). "This suggests that the findings of the SONIC trial may extend to real-world clinical practice, even in patients who had previous IM exposure," the investigators noted.

Combination therapy was also significantly associated with longer time to first IBD-related hospitalization (HR, 0.53) and the need to switch anti-TNF agent (HR, 0.63). However, no such relationships were found for time to resective surgery or corticosteroid use. Choice of agent from either class had no influence on effectiveness of combination therapy.

In contrast with the above findings, combination therapy in patients with UC was less promising, which aligns with previous studies.

"[W]e were not able to demonstrate a significant advantage to combination therapy in persons with UC," the investigators wrote. "In addition, all published cohort studies to date have not been able to confirm a significant benefit to combination therapy in UC. ... In light of the lower quality of prior evidence, combined with the results from our study, the indication for combination therapy in UC would appear to be weaker."

"Further analyses in larger cohorts may clarify whether there is a clinically relevant benefit of combination therapy in persons with UC," the investigators concluded. "Because of the discrepancy between our findings and those of a meta-analysis of cohort studies previously published on this topic, confirmation of our results is required in future studies."

The study was funded by Crohn's and Colitis Canada Grants in Aid of Research and the Helmsley Foundation. The investigators reported financial relationships with AbbVie Canada, Takeda Canada, Merck Canada, and others.

ginews@gastro.org

SOURCE: Targownik LE et al. Clin Gastroenterol Hepatol. 2018 Nov 15. doi: 10.1016/j.cgh.2018.11.003.

Twenty years after the approval of the first anti–tumor necrosis factor (TNF) biologic agent for the treatment of inflammatory bowel disease (IBD), patients and providers are still learning how to optimize these medications. One optimization is the use of combination therapy (immunomodulator and anti-TNF). Immunomodulators are used independently for maintenance of remission of IBD, and they have been shown to reduce immunogenicity and improve efficacy when used in combination with an anti-TNF agent in prior short-term randomized controlled trials. However, use of combination therapy in the real world is not universally practiced. Data are lacking on the risks and benefits of long-term use of these agents. Therefore, this article by Targownik et al. is very timely.


Dr. Long

Patients with Crohn's disease treated with combination therapy in this population-based cohort had improved efficacy including a significant decrease in treatment ineffectiveness, increased time to first hospitalization, and increased time to anti-TNF medication switch. Importantly, a mixed group of patients who had previously been on azathioprine monotherapy and those newly starting this therapy at the time of anti-TNF initiation were included in this cohort (a group similar to what we see in real-world practice). Data on risk factors for disease complications, such as disease phenotype or severity, were not available. By contrast, none of the efficacy associations were improved in the smaller group of patients with ulcerative colitis on combination therapy.

As providers counsel patients on the benefits and risks of various IBD treatment choices, these data by Targownik et al. will inform decisions. Future research should incorporate additional means of biologic optimization, such as the use of therapeutic drug monitoring and/or risk factor–based selection of therapeutic agents, to better inform individualized treatment choices.

Millie D. Long, MD, MPH, AGAF, is an associate professor of medicine in the division of gastroenterology and hepatology; Inflammatory Bowel Diseases Center; vice chief for education; director, Gastroenterology and Hepatology Fellowship Program at the University of North Carolina at Chapel Hill. She has consulted for Takeda, Pfizer, Janssen, UCB, AbbVie, Salix, Valeant, and Target Pharmasolutions, and has received research support from Takeda, Pfizer.

Algorithm predicts villous atrophy in children with potential celiac disease

BY WILL PASS
MDedge News

A new algorithm may be able to predict which children with potential celiac disease will go on to develop villous atrophy, according to investigators writing in the August issue of Gastroenterology.

The risk model was developed from the largest cohort of its kind, with the longest follow-up to date, reported lead author Renata Auricchio, MD, PhD, of University Federico II in Naples, Italy, and colleagues. Using the algorithm, which relies most heavily on a baseline number of intraepithelial lymphocytes (IELs) in mucosa, followed by age at diagnosis and genetic profile, clinicians may now consider prescribing gluten-free diets to only the highest-risk patients, instead of all suspected cases, noting that more than half of potential cases do not develop flat mucosa within 12 years.

Key clinical point
The algorithm correctly classified, at enrollment, 80% of children who did not develop flat mucosa during follow-up.

Development of the algorithm began with enrollment of 340 children aged 2-18 years who were positive for immunoglobulin A endomysial antibodies and had tested positive twice consecutively for antitissue transglutaminase antibodies. Additionally, children were required to possess HLA DQ2- or DQ8-positive haplotypes and have normal duodenal architecture in five biopsy samples. Because of symptoms suggestive of celiac disease or parental discretion, 60 patients were started on a gluten-free diet and excluded from the study, leaving 280 patients in the final cohort. These patients were kept on a gluten-containing diet and followed for up to 12 years. Every 6 months, the investigators checked antibodies and clinical status, and every 2 years, small-bowel biopsy was performed, if symptoms had not necessitated this earlier.

After a median follow-up of 60 months, ranging from 18 months to 12 years, 39 patients (13.9%) developed symptoms of celiac disease and were placed on a gluten-free diet, although they declined confirmatory biopsy, disallowing classification of celiac disease. Another 33 patients (11.7%) were lost to follow-up and 89 (32%) stopped producing antibodies, with none going on to develop villous atrophy. In total, 42 patients (15%) developed flat mucosa during the follow-up period, with an estimated cumulative incidence of 43% at 12 years. The investigators noted that patients most frequently progressed within two time frames; at 24-48 months after enrollment, or at 96-120 months.

To develop the algorithm, the investigators performed multivariable analysis with several potential risk factors, including age, sex, genetic profile, mucosal characteristics, and concomitant autoimmune diseases. Of these, a high number of IELs upon first biopsy was most highly correlated with progression to celiac disease. Patients who developed villous atrophy had a mean value of 11.9 IELs at first biopsy, compared with 6.44 among those who remained potential (P = .05).

'The long-term risks of potential celiac disease have never been accurately evaluated. Thus, before adopting a wait-and-see strategy on a gluten-containing diet, a final decision should always be shared with the family.'

The next strongest predictive factors were age and genetic profile. Just 7% of children less than 3 years developed flat mucosa, compared with 51% of patients aged 3-10 years and 55% of those older than 10 years (P = .007). HLA status was predictive in the group aged 3-10 years but not significant in the youngest or oldest patients. Therefore, HLA haplotype was included in the final algorithm, but with smaller contribution than five non-HLA genes, namely, IL12a, SH2B3, RGS1, CCR, and IL2/IL21.

"Combining these risk factors, we set up a model to predict the probability for a patient to evolve from potential celiac disease to villous atrophy," the investigators wrote. "Overall, the discriminant analysis model allows us to correctly classify, at entry, 80% of the children who will not develop a flat mucosa over follow-up, while approximately 69% of those who will develop flat mucosa are correctly classified by the parameters we analyzed."

The investigators noted that IEL count may be an uncommon diagnostic; however, they recommended the test, even if it necessitates referral. "The [IEL] count turned out to be crucial for the prediction power of the discriminant analysis," the investigators wrote.

"The long-term risks of potential celiac disease have never been accurately evaluated. Thus, before adopting a wait-and-see strategy on a gluten-containing diet, a final decision should always be shared with the family."

Still, the investigators concluded that gluten-free diet "should not be prescribed indistinctly to all patients" with potential celiac disease, as it is a "very heterogenic condition and is not necessarily the first step of overt disease."

The investigators disclosed no funding or conflicts of interest.

ginews@gastro.org

SOURCE: Auricchio R et al. Gastroenterology. 2019 Apr 9. doi: 10.1053/j.gastro.2019.04.004.

While the simplification of the diagnostic process for celiac disease (CD), now heavily reliant on CD-specific autoantibodies, has made the life of clinicians easier in many respects, new scenarios also have emerged that are posing new challenges. One of them is that a substantial, growing portion of subjects (who may or may not have symptoms) present with positive CD autoantibodies but a normal duodenal mucosa ("potential celiac patient"). If left on gluten, with time some will develop villous atrophy, but some won't. What is the clinician supposed to do with them? The paper by Auricchio et al. addresses this issue in a rigorous, well-structured way by closely prospectively monitoring a large series of pediatric patients. Their conclusions have very useful implications for the clinician. In fact taking into consideration several criteria, they found valuable after a long observation period – such as age of the child, HLA status, persistence of elevated CD-specific autoantibodies, and presence or absence of intraepithelial lymphocytes in the initial biopsy – they concluded that one can correctly identify at the beginning four out of five potential celiac patients who will not develop villous atrophy, and thus do not need to follow a gluten-free diet. Ultimately however, let's not forget that we are still dealing with percentages of risk to develop full-blown CD, not with definitive certainties. Hence, the decision of starting a gluten-free diet or not (and of how often and in which way to monitor those who remain on gluten) remains a mutually agreed upon plan sealed by two actors: on one side the patient (or the patient's family); and on the other, an experienced health care provider who has clearly explained the facts. In other words, evidence-based criteria, good old medicine, and a grain of salt!


Dr. Guandalini

Stefano Guandalini, MD, AGAF, is a pediatric gastroenterologist at the University of Chicago Medical Center. He has no conflicts of interest.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Inside AGA's meeting with FDA on fecal microbiota transplantation

AGA's microbiome leaders recently met with representatives from FDA's Center for Biologics Evaluation and Research (CBER) to share clinician and researcher perspectives on fecal microbiota transplantation (FMT) and understand CBER's current thinking on the regulation of FMT for the treatment of *Clostridioides difficile* (*C. difficile*) infection. Here are the key takeaways from AGA's discussion with CBER.

AGA made clear to FDA the needs and concerns of the clinical and research communities regarding FMT. AGA communicated clinician concerns about patient access to whole-stool FMT being restricted or perhaps eliminated once drugs containing live microbials are FDA approved. AGA's representatives also shared concerns about the narrow inclusion criteria for current clinical trials and whether the new drugs will be as effective as whole-stool FMT for vulnerable populations such as the elderly or immunocompromised, who make up the majority of patients with *C. difficile* infection but are often excluded from current trials. Finally, AGA emphasized the need to encourage innovation in product development and the importance of performing controlled safety and efficacy studies on products that can be manufactured predictably and reproducibly.

All stakeholders agreed that the AGA FMT National Registry is an important effort to collect short- and long-term data on the safety and efficacy of FMT. AGA will maintain dialogue with CBER regarding data from the registry and lessons learned. Clinicians practicing FMT are strongly encouraged to participate in the FMT National Registry, which will follow short- and long-term outcomes of patients receiving FMT for up to 10 years. The registry is funded by a grant from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (award number R24 AI118629) and is a partnership of AGA, the Crohn's & Colitis Foundation, the Infectious Diseases Society of America, and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

CBER is currently working on an update to the enforcement discretion policy on the use of FMT for *C. difficile* infection not responsive to standard therapies. Agency representatives noted that all comments will be considered as the agency finalizes the guidance. The current enforcement discretion policy has been in place since July 2013 and was most recently updated by CBER in a draft guidance in March 2016. The policy enables clinicians to use FMT for the treatment of *C. difficile* infection not responsive to standard therapies without having an investigational new drug (IND) application in place.

CBER is interested in hearing ideas for novel trial designs that may help address the challenges of patient recruitment for clinical trials in *C. difficile* infection and other indications for FMT. AGA encourages members to share their thoughts on this topic through the AGA Community.

Human stool will continue to be regulated as a drug and biological product. The agency stated that human stool does not meet the definition of a tissue and FDA does not intend to change how it is currently classified.

CBER is interested in hearing ideas for novel trial designs that may help address the challenges of patient recruitment for clinical trials in *C. difficile* infection and other indications for FMT. AGA encourages members to share their thoughts on this topic through the AGA Community.

Following AGA's meeting with CBER, FDA issued a safety alert because of the death of a patient who died from an FMT containing a multi-drug resistant organism. The agency has since issued additional requirements for IND holders on stool donor screening. AGA will continue to engage with FDA on this issue and share updates as they become available with all members.

Meeting participants from AGA membership included:

- Gail A. Hecht, MD, MS, AGAF, immediate past chair, AGA Center for Gut Microbiome Research and Education Scientific Advisory Board
- Colleen R. Kelly, MD, co-chair, AGA FMT National Registry Steering Committee
- Alexander Khoruts, MD, member, AGA Center for Gut Microbiome Research and Education Scientific Advisory Board
- Gary D. Wu, MD, AGAF, basic research councilor, AGA Institute Governing Board, and member, AGA FMT National Registry Steering Committee

Meeting participants from FDA/CBER included:

- Peter Marks, MD, PhD, Director, CBER
- Celia Witten, PhD, MD, Deputy Director, CBER
- Diane Maloney, JD, Associate Director for Policy, CBER
- Julie Tierney, JD, Senior Policy Advisor for Strategic Planning & Legislation, CBER
- Marion Gruber, PhD, Director, Office of Vaccines Research and Review (OVRR), CBER
- Theresa Finn, PhD, Associate Director for Policy, OVRR, CBER
- Doran Fink, MD, PhD, Deputy Director, Clinical, Division of Vaccines and Related Products Applications, OVRR, CBER
- Paul Carlson, PhD, Senior Staff Fellow, OVRR
- Lorrie McNeill, Director, Office of Communication, Outreach and Development, CBER

This meeting took place on May 6, 2019, at the FDA headquarters in Silver Spring, Md.

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The father of cancer genetics

Dr. Lynch *from page 1*

ana, and his residency in internal medicine at the University of Nebraska College of Medicine. His first faculty appointment was at The University of Texas MD Anderson Cancer Center.

In 1967, he accepted a position at Creighton, in Omaha, Neb., where he would spend the rest of his storied career. Dr. Lynch was a professor at Creighton University School of Medicine, and the founder and director of the Hereditary Cancer Center at Creighton, established in 1984. He served as chair of the institution's Department of Preventive Medicine and Public Health, and was named the inaugural holder of the Charles F. and Mary C. Heider Endowed Chair in Cancer Research at Creighton.

A patient he encountered in 1962 – an alcoholic that drank because he believed he would die of colon cancer since everyone in his family had – was the catalyst for his groundbreaking work into the possibility of a hereditary component to some forms of cancer. During this time, it was understood that carcinogenic chemicals and viruses were the primary cause of cancer.

Dr. Lynch provided the first complete description of hereditary nonpolyposis colorectal cancer, a form of colon cancer eventually renamed Lynch syndrome. He continued his research, eventually identifying a hereditary form of breast and ovarian cancers, melanoma, and prostate and pancreatic cancers. His efforts also resulted in one of the world's largest databases of family cancer histories.

Dr. Lynch passed away on June 2, 2019, at the age of 91. AGA members are sharing their stories and the impact Dr. Lynch had on their work in the AGA Community – https://community.gastro.org/groups/community-home/digestviewer/viewthread?GroupId=25&MessageKey=bf1e1580-0a05-4840-b800-0a436bd8346d).

Lucas Franki contributed to this report.

ginews@gastro.org

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Correct answer: C

Rationale

The two standard treatment regimens for AIH include corticosteroids (prednisone or prednisolone) alone, or corticosteroids combined with azathioprine. The combination regimen allows for a lower dose of steroids and fewer side effects with the same therapeutic efficacy. This patient appears to have developed azathioprine-induced pancreatitis, which is a rare complication more often seen in patients with Crohn's disease treated with azathioprine. In patients who are intolerant of azathioprine, mycophenolate mofetil and calcineurin inhibitors have been used with success.

There are data supporting the use of budesonide in place of prednisone, but this regimen is not as effective in patients with cirrhosis or advanced fibrosis, so it is reserved for patients with lesser degrees of liver fibrosis. The TNF-alpha inhibitors are not used to treat AIH, nor is the IL-1 inhibitor anakinra.

References

1. Czaja AJ. Diagnosis and management of autoimmune hepatitis: Current status and future directions. Gut Liver. 2016;10:177-203.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune Hepatitis. J Hepatol. 2015:63:971-1004.
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Q2. Correct answer: E

Rationale

Radiographic evaluation is commonly employed in the diagnosis and management of patients with lower GI bleeding. CT scans, tagged red blood cell scintigraphy, and angiography all have roles in the care of these patients. Though tagged red blood cell scintigraphy is the most sensitive modality at detecting active bleeding, requiring rates from 0.05-0.1 cc/min, it is relatively poor at localizing the bleeding, accurately predicting the location in only 60%-70% of cases. CT scans have the advantage of being quickly performed and are widely available. If extravasation is seen, its location is also accurately determined. It is not as sensitive as red blood cell scintigraphy, however, and requires bleeding rates of 0.3-0.5 cc/min to be positive. Angiography has the advantage of being both diagnostic and potentially therapeutic. It is best performed in sicker patients with hypotension and high transfusion demands as it is higher yield in these situations. Angiography is the least sensitive of these modalities, requiring bleeding rates between 0.5 and 1 cc/min to be positive.

Reference

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Please contact us for more information at foundation@gastro.org or visit http://gastro.planmylegacy.org/.

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Top AGA Community patient cases

Physicians with difficult patient scenarios 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. In case you missed it, here are the most popular clinical discussions shared in the forum recently:

1. Crohn's disease, Infliximab and liver abscess (http://ow.ly/MehK30p2UZr)
2. Positive Cologuard testing in patient on blood thinners (http://ow.ly/lJXF30p2V12)
3. Recombinant zoster vaccine in IBD patients on biologics (http://ow.ly/FWGA30p2V1F)
4. Hair loss and Crohn's disease (http://ow.ly/C6Sa30p2V2h)

Access these clinical cases and more discussions at https://community.gastro.org/discussions.

AGA journals select new editorial fellows

The AGA journals – *Gastroenterology*, *Clinical Gastroenterology and Hepatology* (*CGH*), and *Cellular and Molecular Gastroenterology and Hepatology* (*CMGH*) – are pleased to announce their 2019-2020 editorial fellows.

Gastroenterology

- Feng Su, MD
  University of Washington, Seattle • @FengSu_MD
- Victoria Weis, PhD
  Wake Forest School of Medicine, Winston-Salem, N.C.

CGH

- Austin Chiang, MD, MPH
  Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia
  @AustinChiangMD
- Jennifer Kolb, MD
  University of Colorado Anschutz Medical Campus, Aurora

CMGH

- Cambrian Liu, PhD
  The Saban Research Institute, Children's Hospital Los Angeles
- Tirthadipa Pradhan-Sundd, PhD
  University of Pittsburgh, Pennsylvania • @Tirthadipa

The editorial fellows will be mentored on their respective journals' editorial processes, including peer review and the publication process from manuscript submission to acceptance. They will participate in discussions and conferences with the boards of editors and work closely with the AGA editorial staff. Additionally, the fellows will participate in AGA's new reviewer education program and will also be offered the opportunity to contribute content to their respective journals. The newly expanded program builds on the success of the previous 2 years when *Gastroenterology* had an editorial fellow.

The journals' board of editors and editorial staff congratulate the fellows.

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➤IBD AND INTESTINAL DISORDERS

CAG Clinical Practice Guideline: Luminal Crohn's disease

BY CALEB RANS
MDedge News

The Canadian Association of Gastroenterology has released a new clinical practice guideline for the treatment of luminal Crohn's disease (CD) in adults.

"In the last decade, treatment paradigms have changed, recognizing that certain clinical parameters carry an increased risk of progressive and disabling disease," wrote Remo Panaccione, MD, of the University of Calgary (Alta.) and collaborators. Dr. Panaccione is the lead author of this practice guideline copublished in Clinical Gastroenterology and Hepatology and the Journal of the Canadian Association of Gastroenterology.

The expert consensus panel consisted of 20 voting members, including both academic and community gastroenterologists, in addition to a specialist nurse practitioner. Other nonvoting members included two GRADE (Grading of Recommendation Assessment, Development, and Evaluation) experts, lay observers, and a patient representative.

The panel systematically reviewed the body of literature for studies related to the management of CD in adults. After applying the search criteria, the team found that the majority of evidence was extracted from systematic reviews and meta-analyses of randomized trials.

Quality of evidence and risk of bias were assessed using the GRADE methodology. The quality of evidence for each consensus statement was classified as either high, moderate, low, or very low, based on the methodology's criteria.

The new guideline provides evidence-based recommendations about optimal treatment approaches for patients with mild to severe active luminal CD in an ambulatory setting, with particular focus on six major drug classes.

The consensus statements were finalized at a face-to-face meeting in Toronto held in September 2016. Prior to completion, a web-based system was used to allow for anonymous voting on level of agreement for each consensus statement.

The new guideline provides evidence-based recommendations about optimal treatment approaches for patients with mild to severe active luminal CD in an ambulatory setting, with particular focus on six major drug classes, including corticosteroids, biologic therapies, immunosuppressants, 5-aminosalicylate, antibiotics, and other therapies.

The consensus group recommended against the use of 5-aminosalicylate or antibiotics as induction

Continued on page 17

Pediatric luminal Crohn's disease guideline issued

BY CALEB RANS
MDedge News

A new clinical practice guideline for the treatment of luminal Crohn's disease (CD) in children has been released by the Canadian Association of Gastroenterology.

The new guideline provides evidence-based recommendations regarding optimal medical treatment strategies for achieving clinical remission based on a multi-item assessment of disease activity in pediatric patients with luminal CD. The guideline does not address surgical management, diagnosis, psychosocial therapies, preventative health considerations, or growth monitoring.

"The implications of inadequately treated CD are of particular importance in children because of the potentially serious and irreversible consequences," wrote David R. Mack, MD, of the University of Ottawa and associates. Dr. Mack is the lead author of the pediatric practice guideline copublished in Gastroenterology and the Journal of the Canadian Association of Gastroenterology.

The consensus group reached its recommendations based on a systematic review of the literature for studies related to the medical treatment of pediatric CD. The majority of studies were randomized trials conducted in adults with CD.

"Evidence of efficacy of specific treatments in achieving mucosal healing is limited; therefore, "complete" or "deep" remission (clinical remission plus mucosal healing) was not the chosen primary outcome," the guideline authors wrote.

The panel recommended that corticosteroids can be used as induction therapy in children with moderate to severe disease. Moreover, budesonide may be an appropriate alternative for induction therapy in patients with mild to moderate CD.

No consensus was reached on the adjuvant use of immunosuppressants during initiation therapy with a biologic drug, but the consensus panel recommended against the use of thiopurine combinations in male patients. Furthermore, no consensus was reached on the role of vedolizumab or antibiotics for induction or maintenance therapy, methotrexate for induction therapy, and the function of aminosalicylates in patients with mild CD.

In contrast, the group recommended against the use of corticosteroids as maintenance therapy, largely because of adverse events reported with long-term use.

At diagnosis or initial stages of severe disease, as well as in patients who have failed with immunosuppressant and corticosteroid induction strategies, enteral nutrition should be used exclusively for induction therapy. In addition, anti–tumor necrosis factor biologics are an appropriate option for induction and maintenance therapy in these patients, according to the guideline.

"The group recommended against the use of oral 5-aminosalicylate for induction or maintenance therapy in patients with moderate disease, and recommended against thiopurines for induction therapy," they wrote.

With respect to cannabis-based products, the panel made a strong recommendation against the use of these agents in all pediatric patients.

In terms of assessment, the team recommended that patients in clinical remission receiving methotrexate or a thiopurine agent as maintenance therapy should be evaluated for mucosal healing within 1 year of therapy initiation.

No consensus was reached on the adjuvant use of immunosuppressants during initiation therapy with a biologic drug, but the consensus panel recommended against the use of thiopurine combinations in male patients. Furthermore, no consensus was reached on the role of vedolizumab or antibiotics for induction or maintenance therapy, methotrexate for induction therapy, and the function of aminosalicylates in patients with mild CD.

The panel highlighted the importance of incorporating patient perspectives into treatment decision making.

"It is hoped that the available information will enhance the discussion between the clinician and the patient and enable the patient to make an evidence-based informed decision."

The expert consensus was made up of 15 voting members that consisted of pediatric gastroenterologists throughout the United States and Canada, with expertise in several domains, including clinical epidemiology, nutrition, health services research, and patient engagement.

Quality of evidence and risk of bias was assessed using the GRADE (Grading of Recommendation Assessment, Development, and Evaluation) criteria. The quality of evidence for each consensus statement was denoted as either high, moderate, low, or very low, based on the criteria.

The consensus statements were finalized at an in-person meeting conducted in Toronto in October 2017.

The guideline was supported through grant funding provided by AbbVie and Takeda. The authors reported financial affiliations with AbbVie and Takeda, as well as Janssen, Nestle Health Sciences, Shire, and several others.

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SOURCE: Mack DR et al. Gastroenterology. 2019. doi: 10.1053/j.gastro.2019.03.022.

Continued from page 14

or maintenance treatment strategies. Alternatively, they suggested that corticosteroids, including budesonide, could be used as induction therapy, but not as maintenance therapy.

"Parenteral methotrexate was proposed for induction and maintenance therapy in patients with corticosteroid-dependent CD," they wrote.

With respect to immunosuppressive therapy, thiopurine agents could be an appropriate option for maintenance therapy in certain low-risk patients, but were not recommended as induction therapy, according to the guideline.

In patients who fail with conventional induction therapies, Dr. Panaccione and colleagues recommended that biological treatments, including ustekinumab, vedolizumab, and anti–tumor necrosis factor agents, could be used. No consensus was reached on the concomitant use of immunosuppressants and biologics.

In recent years, an increasing amount of evidence has emphasized the importance of mucosal healing as a key goal of therapy. In particular, the use of some therapies can result in mucosal healing and symptomatic improvement in certain patients with luminal CD.

In addition, the authors explained that mucosal healing has been linked to better clinical outcomes over the short and long term. As a result, the recommendations in the guideline target complete remission, defined as both endoscopic and symptomatic remission.

"The outcome assessed in most randomized controlled trials (RCTs) has been either symptomatic remission or symptomatic response, with only more contemporary clinical trials including endoscopic outcomes," the guideline authors wrote.

For this reason, the GRADE criteria–based quality of evidence for some of the consensus statements had to be lowered, they noted.

The panel acknowledged the importance of incorporating patient perspectives into treatment decision making; however, they reported that many gaps in clinical practice still remain.

"In many instances, factors that influence patient decisions relating to therapy choice and goals of therapy are not the same as those of the treating clinician," they wrote. "[Current] surveys indicate a discrepancy between patient and physician treatment goals."

In response, the guideline authors highlighted the importance of improved patient-physician collaboration and patient education.

The guideline was supported through grant funding provided by AbbVie, Janssen, Pfizer, and Takeda. The authors reported financial affiliations with AbbVie, Amgen, Baxter, Janssen, Shire, Takeda, and several others.

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SOURCE: Panaccione R et al. Clin Gastroenterol Hepatol. 2019 Mar 7. doi: 10.1016/j.cgh.2019.02.043.

Diagnosis and management of gastric intestinal metaplasia in the United States

BY DIANA CURRAS-MARTIN, MD, AND SUSANA GONZALEZ, MD

Introduction

Despite a global decline in the incidence of gastric cancer over the past 3 decades, it remains the fifth most commonly diagnosed cancer and the third most common cause of cancer deaths worldwide.[1] In the United States it is the fourth most commonly diagnosed GI malignancy, after colorectal, pancreas, and liver cancer. The prevalence remains high in Latin America and Asia, which has implications in the United States because of growing Hispanic and Asian populations.[2,3] In recent years, a change in the trend of gastric cancer among non-Hispanic whites has been observed, particularly in women younger than 50 years old.[4] Gastric intestinal metaplasia has been recognized worldwide as a premalignant precursor to gastric cancer, but currently, there are limited U.S. guidelines, leading to controversy over management of this condition.[5]

Gastric intestinal metaplasia (GIM) is being identified frequently on upper endoscopy, often incidentally on biopsies performed for other indications. However, given limited U.S. guidelines on this topic, there remains controversy surrounding management of these patients after GIM discovery.

In the In Focus article for this quarter, which is brought to you by *The New Gastroenterologist*, Diana Curras-Martin and Susana Gonzalez provide an enlightening overview of GIM in which they review the risk factors and types of GIM, classifications of GIM, as well as who should be screened and how screening should be done. As GIM will continually be identified in practice, understanding the nuances of managing this condition is a must for all GIs.

Bryson W. Katona, MD, PhD
Editor in Chief, The New Gastroenterologist

Etiology

Gastric adenocarcinomas are classified into two subcategories based on location (cardia and noncardia) and histology (intestinal and diffuse types).[6,7] Atrophic gastritis and gastric intestinal metaplasia (GIM) are considered precursors of intestinal-type noncardia gastric adenocarcinoma. The Correa cascade is a commonly accepted precancer sequence for noncardia gastric adenocarcinoma that describes mucosal changes from inflammation to atrophy to metaplasia to intraepithelial neoplasia and culminating in carcinoma.[8,9] It has been observed that GIM may be the histologic change prior to the development of dysplasia and over 50% of patients with high-grade dysplasia will progress to adenocarcinoma.[10-12] In the United States, GIM has the highest prevalence in African Americans, Hispanics, and East Asians, with the overall GIM prevalence regardless of ethnicity reported from 3.05% to 19.2%.[5,13]

Risk factors and subclassification

Replacement of the foveolar and/or glandular epithelium in the oxyntic and antral mucosa by intestinal epithelium results in GIM. It can be focal when limited to one region of the stomach or extensive when two or more regions are involved.[14] The main risk factors for GIM development are *Helicobacter pylori* infection, tobacco, alcohol consumption, high salt intake, and chronic bile reflux.[15,16] Additional risks for developing gastric cancer include older age, certain ethnicities, and male sex.[17]

CagA strains of *H. pylori* can promote carcinogenesis by inducing a mitogenic cellular response and downregulating cell adhesion.[18,19] Less carcinogenic risk is associated with *H. pylori* Cag-A negative strains; however, they also have oncogenic potential mediated by expression of babA2 and vacA genes.[20] Hence, the combination of multiple virulent factors encoded in babA2, CagA, and vacA genes has been associated with increased risk of GIM, inflammation, and development of gastric cancer.[15] The clinical usefulness of genotyping *H. pylori* strains specifically to survey precancerous gastric lesions remains to be seen because of a lack of sufficient clinical studies. In addition, genotyping *H. pylori* is not commonly performed as part of clinical practice.

The loss of parietal cells seen in atrophic gastritis due to chronic

The combination of multiple virulent factors encoded in babA2, CagA, and vacA genes has been associated with increased risk of GIM, inflammation, and development of gastric cancer.

H. pylori infection has been linked to the development of metaplasia due to possible loss of differentiation-promoting factors. As a result, metaplastic cells emerge that express spasmolytic polypeptide (SP or TFF2); hence, this type of metaplasia is referred to as spasmolytic polypeptide–expressing metaplasia (SPEM). The cellular mechanism that may explain a precursor role of SPEM in the development of GIM remains unknown.[14] A second competing theory for the development of GIM is the clonal expansion of stem cells in the gastric isthmus that can lead to dysplasia and cancer development.[14]

On the basis of histological similarities with small intestinal or colonic epithelium, GIM can be further classified into complete or incomplete intestinal metaplasia.[21] Complete intestinal metaplasia most closely resembles small intestinal epithelium with a brush border and goblet cells. Incomplete intestinal metaplasia resembles the colonic epithelium and lacks a brush border. A second classification further classifies GIM into three subtypes: Type I contains nonsecretory absorptive cells and sialomucin secreting goblet cells; type II has few absorptive cells, columnar cells secreting sialomucin, goblet cells secreting mainly sialomucin but some sulphomucin, and presence of Paneth cells; and type III consists of columnar cells secreting predominantly sulphomucin, goblet cells secreting sialomucin or sulphomucin, and absence of Paneth cells.[15,22] In this subclassification, type I GIM is known as complete GIM and types II and III as incomplete GIM.[23-25]

Multiple studies performed outside of the United States have shown a higher progression risk to gastric adenocarcinoma in in-

Dr. Curras-Martin is an internal medicine resident at Hackensack Meridian Jersey Shore University Medical Center. **Dr. Gonzalez** is assistant professor of medicine in the division of gastroenterology and hepatology (@WCM_GI), Weill Cornell Medicine, New York Presbyterian Hospital–Cornell.

complete intestinal metaplasia, or type III intestinal metaplasia.[26-32] Also, the risk of gastric cancer has been demonstrated to be higher among patients with a greater area of metaplasia and extensive intestinal metaplasia, defined as GIM in both the antrum and corpus.[33,34] Hence, the extent of the metaplasia determined with mapping biopsies, regardless of the subtype, should also be incorporated into the risk assessment of the patient. Currently, a major limitation in the United States is a standardized method of pathologic reporting including subclassification of incomplete versus complete intestinal metaplasia.

Which patients to screen

Understanding this sequence of carcinogenesis offers a potential window for screening and surveillance. Subsequently, early detection of precancerous mucosal changes would be more amenable for endoscopic submucosal dissection (ESD).[35,36] Currently, U.S. society guidelines do not specifically address the management of GIM. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines for management of premalignant and malignant conditions of the stomach recommend surveillance in individuals with a family history of gastric cancer or of high-risk ethnic background but with no specific optimal surveillance interval.[37] Also, *H. pylori* treatment is recommended if identified, but empiric treatment in GIM was felt to be controversial. The AGA recently sought comments on a proposed new guideline for the management of GIM. This guideline should be released after the comment period and help address management of GIM in the United States. In April of 2019, the European Society of Gastrointestinal Endoscopy (ESGE) updated the management of epithelial precancerous conditions and lesions in the stomach (MAPS II) guideline.[38] The MAPS II guideline identifies atrophic gastritis and intestinal metaplasia as precancerous lesions. In patients with moderate to marked atrophy or GIM affecting both antral and body mucosa, ESGE recommends endoscopic surveillance with high-definition chromoendoscopy, mapping, and guided biopsies or at least two biopsies taken separately at the lesser and greater curvature of the antrum and body. *H. pylori* eradication was recommended if the patient tested positive.

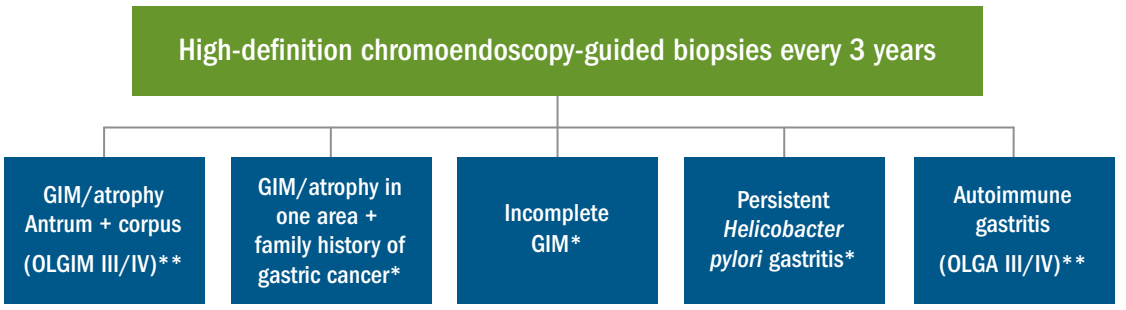
Furthermore, MAPS II proposed replacing atrophic gastritis (AG) in the Operative Link on Gastritis Assessment (OLGA) staging by GIM (OLGIM) as it is considered a more reliable predictor of an individual's gastric neoplasia risk, based on the interobserver agreement kappa value 0.6 for AG versus 0.9 for GIM.[39] Five biopsies (two from the antrum, two from the corpus, and one from the incisura angularis) are needed for the OLGA/OLGIM score system to be considered an accurate predictor of this risk.[39] This is supported by the early findings of gastric atrophy and GIM in the incisura angularis.[23] In addition, for patients with GIM only in either the antrum or the body, a family history of gastric cancer, incomplete GIM, autoimmune gastritis, or persistent *H. pylori* infection was felt to increase the risk to warrant surveillance every 3 years. In those patients with atrophy or GIM in both the antrum and body with a first-degree relative with gastric cancer, surveillance was recommended every 1-2 years. Patients with any dysplasia and a visible lesion should have staging and resection. With no visible lesion, a follow-up endoscopy should be performed in 6 months with high-grade dysplasia and with low-grade dysplasia a repeat in 12 months. Patients with mild to moderate atrophy in the antrum and no intestinal metaplasia were not felt to warrant any further surveillance. (See Figure 1.)

A recent study explored the cost-effectiveness of noncardia gastric cancer screening in the United States stratified by race or ethnicity with a time horizon of 30 years. The study determined that performing endoscopic screening with mapping biopsies in high-risk patients (non-Hispanic black, Hispanic, and Asian individuals) from 50 years of age with continued surveillance only when indicated would be cost effective compared to a no-screening strategy. These patients had sampling performed via an updated Sydney protocol. If GIM was found, the patients would be enrolled into a 3-year surveillance program. Whereas if dysplasia was present, the patients would undergo endoscopic submucosal dissection or surgical resection and continue a postresection surveillance schedule.[40,41]

A recent study determined that performing endoscopic screening with mapping biopsies in high-risk patients from 50 years of age with continued surveillance only when indicated would be cost effective compared to no screening.

Figure 1

Surveillance recommendations according to MAPS II, April 2019



*Low-quality evidence. Weak recommendation

**Moderate-quality evidence. Strong recommendation

Courtesy Dr. Curras-Martin and Dr. Gonzalez

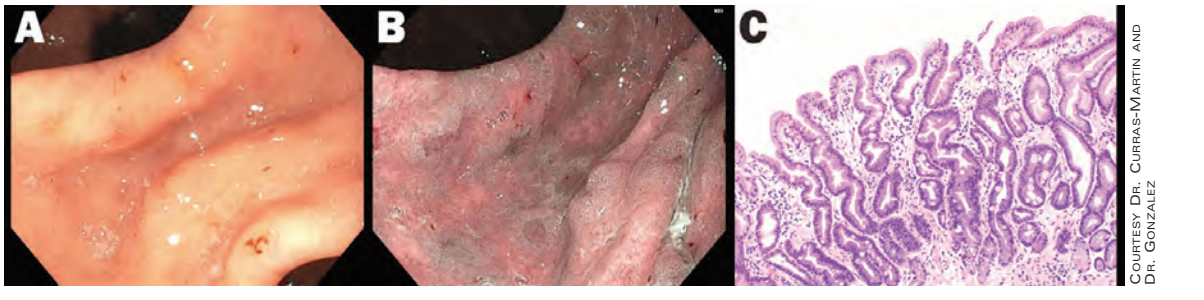
How to screen

Previous studies have found a poor correlation between the endoscopic determination of gastric atrophy and the histologic diagnosis.[42] Several studies also found that gastric cancer was missed on initial endoscopic examinations. Sensitivity of endoscopy to detect gastric cancer has ranged from 77% to 93%.[43,44] In the United States, there is a lack of standardized quality indicators for upper endoscopy exams. The ESGE has suggested several performance measures to ensure a quality endoscopy exam, including accurate photo documentation, sufficient procedure time of at least 7 minutes, adherence to biopsy protocols, and low complication rates.[45] In Asia, a systematic screening protocol is used for photo documentation, and simple techniques such as adequate air insufflation and irrigation to remove mucus are routinely used to improve the endoscopy exam.[46,47] The mean time of an endoscopy exam has also been found to increase the detection of neoplastic lesions, as slow endoscopists – with a mean exam duration of 8.6 ± 4.2 min during upper endoscopy – detected threefold more neoplastic lesions than did fast endoscopists.[48]

A standardized biopsy approach is also important when screening patients. The updated Sydney protocol has been suggested for mapping the stomach to screen for atrophy and GIM. This protocol recommends two biopsies from the antrum (at the lesser and greater curvature), two from the body (at the lesser and greater curvature),

Continued on following page

Figure 2



Courtesy Dr. Curras-Martin and Dr. Gonzalez

A. High-definition white-light endoscopy shows patient with diffuse gastric intestinal metaplasia. B. NBI image of patient with diffuse GIM shows ridge and villous appearance. C. High-powered H&E of biopsy shows intestinal metaplasia.

Continued from previous page

and one from the incisura.[23] This biopsy protocol was also suggested in the recent MAPS II update, with the biopsy of the incisura felt to be an additional biopsy left to the discretion of the endoscopist. Notably, abnormal appearing mucosal areas should be biopsied separately from the mapping biopsies.

High-definition endoscopy with virtual chromoendoscopy is felt to be better than white-light endoscopy alone at detecting precancerous gastric lesions.[38] (See Figure 2.)

In particular, narrow-band imaging (NBI) has been studied and found to increase the diagnostic yield of GIM and dysplasia compared with white light alone.[49]

Narrow-band imaging, in particular, has been studied and found to increase the diagnostic yield of GIM and dysplasia compared with white light alone.

Several studies have shown an increased accuracy for the detection of GIM with magnification NBI.[50-52] An unfortunate limitation is the geographic availability of magnification NBI: It is not available in the United States. A multicenter study in Portugal developed a new classification system for the appearance of precancerous lesions with NBI and tested its accuracy in endoscopists with a wide range of NBI experience. An abnormal mucosal pattern that showed light blue crests/regular ridge or a tubulovillous appearance and a regular mucosal pattern was found with GIM. An irregular vascular pattern with a white opaque substance and an absent or irregular mucosal pattern was most often found with dysplasia. Furthermore, the reproducibility of these patterns was high between endoscopists.[53] Multiple studies have been performed on additional imaging technologies to enhance the detection of gastric neoplasia; however, these technologies are still investigational and currently not recommended for screening.[54-57]

Serum pepsinogens have been studied in Europe and Asia as noninvasive indicators of gastric atrophy to determine who should be screened with endoscopy.[58] A low serum pepsinogen I level below 70 ng/mL and pepsinogen I/II ratio below 3 has generally been used to detect atrophic gastritis and at-risk populations. However, the studies performed in Europe and Asia used different methods for quantifying pepsinogen levels. Therefore, cutoff values cannot be generalized for all assays and should be validated for the specific tests used.[38]

Summary

Gastric atrophy and gastric intestinal metaplasia are considered precancerous lesions with an increased risk of development of gastric cancer. *H. pylori* is a major risk factor for the development of GIM. The extent of GIM as well as the presence of incomplete intestinal metaplasia, or type III intestinal metaplasia has been found to have the highest gastric cancer risk. Currently, in the United States, specific guidelines on endoscopic screening and surveillance for noncardia gastric adenocarcinoma based on histological subtype of GIM, location, and extension are lacking. The ESGE recently updated guidelines that recommend surveillance of patients with extensive atrophy and intestinal metaplasia or with a significant family history. Location and extension of intestinal metaplasia plays a role in increased risk. Screening should include a standardized upper endoscopy approach with high-definition white-light endoscopy and NBI, at least a 7-minute examination, adequate insufflation and cleaning, adequate photo documentation, and a standardized biopsy protocol. Further studies are needed to determine an appropriate surveillance interval and standardized pathology reporting approach as well.

See references at www.mdedge.com/gihepnews/new-gastroenterologist.

Behavioral treatment

NAFLD *from page 1*

ing behavioral weight loss programs, pharmacotherapy, or bariatric surgery, alone or in combination. To limit confounding, the investigators excluded studies combining weight loss with other treatments, such as medications. Weight loss interventions were compared to liver disease outcomes associated with lower-intensity weight loss intervention or none or minimal weight loss support, using at least one reported biomarker of liver disease.

The literature search returned 22 eligible studies involving 2,588 patients. The investigators found that more-intensive weight loss programs were associated with greater weight loss than lower-intensity methods (–3.61 kg; I^2 = 95%). Multiple biomarkers of liver disease showed significant improvements in association with formal weight loss programs, including histologically or radiologically measured liver steatosis (standardized mean difference: –1.48; I^2 = 94%), histologic NAFLD activity score (–0.92; I^2 = 95%), presence of nonalcoholic steatohepatitis (OR, 0.14; I^2 = 0%), alanine aminotransferase (–9.81 U/L; I^2 = 97%), aspartate transaminase (–4.84 U/L; I^2 = 96%), alkaline phosphatase (–5.53 U/L; I^2 = 96%), and gamma-glutamyl transferase (–4.35 U/L; I^2 = 92%). Weight loss interventions were not significantly associated with histologic liver fibrosis or inflammation, they noted.

"The accumulated evidence supports changing the clinical guidelines and routine practice to recommend formal weight loss programs to treat people with NAFLD," the investigators concluded.

The study was funded by the National Institute for Health Research Oxford Biomedical Research Centre and the Oxford NIHR Collaboration and Leadership in Applied Health Research. The investigators reported grants for other research from Cambridge Weight Plan.

ginews@gastro.org

SOURCE: Koutoukidis DA et al. JAMA Int Med. 2019 Jul 1. doi: 10.1001/jamainternmed.2019.2248.

AGA Resource

The AGA Practice guide on Obesity and Weight management, Education and Resources (POWER) paper provides physicians with a comprehensive, multidisciplinary process to guide and personalize innovative obesity care for safe and effective weight management. Learn more at https://www.gastro.org/practice-guidance/practice-updates/obesity-practice-guide.

Clear support for weight loss programs

Past studies have attempted to investigate the relationship between weight loss and nonalcoholic fatty liver disease (NAFLD), but they did so with various interventions and outcomes measures. Fortunately, the study by Dr. Koutoukidis and colleagues helps clear up this variability with a well-conducted systematic review. The results offer a convincing case that formal weight loss programs should be a cornerstone of NAFLD treatment, based on improvements in blood, histologic, and radiologic biomarkers of liver disease. Since pharmacologic options for NAFLD are limited, these findings are particularly important.

Although the study did not reveal improvements in fibrosis or inflammation with weight loss, this is likely due to the scarcity of trials with histologic measures or long-term follow-up. Where long-term follow-up was available, weight loss was not maintained, disallowing clear conclusions. Still, other studies have shown that sustained weight loss is associated with improvements in fibrosis and mortality, so clinicians should feel encouraged that formal weight loss programs for patients with NAFLD likely have life-saving consequences.

Elizabeth Adler, MD, and Danielle Brandman, MD, are with the University of California, San Francisco. Dr. Brandman reported financial affiliations with Conatus, Gilead, and Allergan. Their remarks are adapted from an accompanying editorial (JAMA Int Med. 2019 Jul 1. doi: 10.1001/jamainternmed.2019.2244).

What in the ACA is severable?

Court *from page 1*

allowed ACA components to be severed if such sectioning was acceptable.

"Congress could have included a severability clause when it adopted the ACA in 2010. Couldn't it have done so?" Judge Engelhardt asked during oral arguments. "It seems like it did the opposite, where it said, 'This is a complete overhaul,' and it set forth a bunch of factual findings. Couldn't Congress have said, 'Oh by the way, we think all of these provisions are such excellent ideas and helpful to the public that if any go by the wayside, then we would want the remainder to continue to apply'?"

Ms. Keith

Congress's silence on the severing of the ACA does not create a presumption against parsing of the law, argued Mr. Siegel, who is representing the Democratic states suing to retain the ACA in *Texas v. United States*. He emphasized that, in 2017, when Congress terminated the individual mandate penalty, it chose not to repeal preexisting protections or other important reforms instituted by the ACA.

"With that action, your Honor, Congress expressed its views that the individual marketplace and indeed the entire Affordable Care Act can operate without an enforceable individual mandate," Mr. Siegel said. "We think that's all this court needs to know to resolve the severability question."

However, Appellate Judge Jennifer Elrod, a President George W. Bush appointee to the court, questioned whether legislators zeroed out the mandate penalty because they knew the law could not survive without the core provision. She surmised that Congress might have assumed, "Aha, this is the silver bullet that's going to undo Obamacare."

Kyle Hawkins, an attorney representing the Republican-led plaintiff states, meanwhile, argued the text of the ACA clearly declares the individual mandate essential to the law and to the goals that Congress intended to achieve.

"The Obama administration thought of that as an inseverable clause," Mr. Hawkins argued. "The district court directly synthesized those considerations ... and it reached the correct conclusion: The individual mandate is unconstitutional and it is inseverable from the remainder of the law."

Texas v. United States stems from a legal challenge by a group of 18 Republican state attorneys general and two individuals in 2018 who argue the ACA should be declared unconstitutional. The plaintiffs say that, because budget legislation in 2017 effectively eliminated the penalty associated with the mandate, the requirement itself is invalid. Without the mandate, the entire law must fall, the plaintiffs contend. The Department of Justice declined to fully defend the law, so 16 Democratic state attorneys general intervened. In December 2018, a district court declared the entire ACA to be invalid, a decision immediately appealed to the 5th U.S. Circuit Court of Appeals by the Democratic attorneys general.

The Trump administration initially agreed that the mandate was unconstitutional and should be parsed. Attorneys for the administration said, if the mandate is found unconstitutional, the court should also consider finding two other provisions – the guaranteed issue and community rating requirements – of the ACA invalid. At the time, the Trump administration said the remainder of the ACA can stand without the three linked provisions. The administration later shifted its stance and asserted that much of the ACA should fall because provisions of the law cannot be severed. However, the DOJ expressed support in keeping some provision intact, such as certain criminal statutes that prevent health care fraud.

Mr. Henneke

Most recently, the DOJ has indicated that, if the ACA is struck down or severed, the decision should apply only in the 18 plaintiff states and not to the entire nation. The fickle position of the Trump administration was questioned during the Court of Appeals hearing with judges asking DOJ attorney August Flentje to clarify why a final ruling should not apply nationwide.

"A lot of this stuff would need to get sorted out," Mr. Flentje responded. "And it's complicated. How it applies in the states and which parts can't be applied at all because they would injure the states ... that raises a lot of complicated issues which I think [will be determined after] a final resolution."

By their line of questioning, the appellate panel appeared to lean toward the plaintiffs' position more so than toward the defendants', said Katie Keith, an attorney and health law analyst who writes about *Texas v. United States* for the Health Affairs Blog.

"At least two of the three judges – the only two that were asking questions – seem very inclined to at, a minimum, strike down the individual mandate itself," Ms. Keith said in an interview. "The conventional wisdom had been that this court would overturn the lower court's decision, and I think folks are walking away, myself included, from oral arguments feeling less certain that that's going to happen."

Robert Henneke, general counsel for the American Future at the Texas Public Policy Foundation, said that plaintiffs "had a good day in court" and that the defendants' arguments seemed to "hit a thud with the judges." Mr. Henneke represents two individual plaintiffs from Texas in the lawsuit.

Bobak Ha'Eri/Wikimedia Commons/CC BY 3.0

"Obamacare is still unconstitutional, and the three-judge panel seemed to agree with the trial court that the entirety of the law should be struck down," Mr. Henneke said in a press conference after oral arguments. "The court really seemed skeptical with the arguments of the other side. We had the chance to tell the story of my clients and how they continue to be hurt by the Affordable Care Act."

Whichever way the Court of Appeals rules, the losing party is expected to appeal to the U.S. Supreme Court, Ms. Keith said. If justices accept the case, a decision could arrive in the summer of 2020, which would coincide with the presidential election. Another option is for the appellate court to send the case back to the lower court for further review, particularly to clear up the DOJ's murky position, Ms. Keith said.

"They might send it back to [the lower court] and say there's some questions here about what's severable," she said. "The DOJ sort of struggled to explain what they're talking about. So they could remand the case back to Judge [Reed Charles] O'Connor to say, 'Figure this out. Work with the parties.' That's an option."

A decision by the Court of Appeals is expected in the next 2 months.

agallegos@mdedge.com

AGA Resource

AGA calls on Congress to enact legislation that contains essential patient protections and other improvements to ensure affordability, accessibility, and quality health care for all Americans. Learn more at https://www.gastro.org/advocacy-and-policy/issues-and-news/top-issues/patient-protections-and-access-to-care.

Deep sedation did not improve adenoma detection

BY JIM KLING
MDedge News

Deep sedation during colonoscopy did not confer any improvement in the detection rate for adenomas or polyps in average-risk patients, based on results from a retrospective analysis at a single institution that switched from moderate to deep sedation.

There remains a question as to whether moderate sedation, such as benzodiazepine plus opioids, might affect adenoma detection rate (ADR). The issue is important in part because of the recent push to use propofol in outpatient colonoscopy clinics, according to Erica Turse, DO, MPH, of the University of Missouri–Columbia, and colleagues.

Previous studies looking at moderate versus deep sedation have yielded mixed results, possibly as a result of confounding arising from mixed patient populations and conditions.

A strength of the study was that the populations in both the moderate- and deep-sedation groups were similar.

The current study, published in Gastrointestinal Endoscopy, aimed to eliminate potential confounders by focusing only on average-risk index colonoscopies, with similar patient populations in both groups.

The researchers examined data from a tertiary care outpatient center at the University of Missouri, which switched from moderate to deep sedation in the spring of 2016. Moderate sedation was achieved using midazolam and fentanyl, and propofol was later used for deep sedation. The study included a total of 585 colonoscopies, with 338 patients in the moderate-sedation group and 247 in the deep-sedation group. The overall polyp detection rate (PDR) was 70.1%, and the ADR was 41.7%.

The two groups did not significantly differ in PDR (71.9% moderate vs. 67.6% deep, $P = .27$) or ADR (44.1% vs. 38.5%; $P = .18$). Among women, there was no difference in PDR (69.3% vs. 64.8%; $P = .41$) or ADR (42.2% vs. 32.4%; $P = .09$). Among men, the results were the same (PDR, 75.3% vs. 71.4%; $P = .56$; ADR, 46.6% vs. 46.7%; $P = 1.0$).

A strength of the study was that the populations in both the moderate- and deep-sedation groups were similar. A weakness is that the study was conducted at a single center. The authors called for a randomized, controlled trial to gain more insight into the benefits of moderate versus deep sedation.

The study had no external funding; the authors had no conflicts of interest.

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SOURCE: Turse E et al. Gastrointest Endosc. 2019 May 15. doi: 10.1016/j.gie.2019.05.011.

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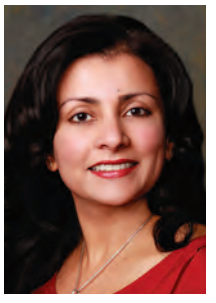
Are next-generation therapies for IBD ready?

BY UMA MAHADEVAN, MD, AGAF

Infliximab was approved by the Food and Drug Administration for Crohn's disease (CD) in 1998. In the following 20 years, there were eight new biologic or small-molecule agents approved for inflammatory bowel disease (IBD), with dozens more in the pipeline. These new mechanisms of action include janus kinase (JAK) inhibition, sphingosine 1 phosphate receptor 1 modulation, anti-integrins, and inhibition of the p19 subunit of IL-23.

Recent studies have tried to address which agent is most appropriate for which patient. First, we must define the endpoints of therapy – endoscopy, histology, or patient-reported outcomes? Then we need to understand how to achieve these endpoints. Combined immunosuppression with infliximab and azathioprine was superior to each alone in the SONIC trial (N Engl J Med. 2010;362:1383-95). The CALM study (Lancet. 2018;390:2779-89) looked at clinical management (escalation in therapy for moderate to severe CD by Crohn's Disease Activity Index and prednisone use versus a treat-to-target approach which responded to C-reactive protein and fecal calprotectin). The treat-to-target approach was more likely to achieve endoscopic response at week 48 (45.9% vs. 30.3%). Early immunosuppression is also more likely to reduce hospitalization and surgery rates as shown in the REACT Trial (Lancet 2015;386:1825-34). This year at Digestive Disease Week®, we can also add the VARSITY trial (Abstract 416A) which was a head-to-head comparison of vedolizumab to adalimumab for UC. Vedolizumab was more likely to induce clinical remission at week 52 than adalimumab, suggesting vedolizumab should be preferred as the first-line biologic in moderate to severe outpatient UC, particularly given its good safety profile.


Dr. Mahadevan

Ustekinumab is FDA approved for CD. At this year's DDW we saw that it is effective for induction and maintenance of remission in UC (Abstract 833) and also has an excellent safety profile. For JAK inhibitors adverse events of interest have included herpes zoster and thromboembolic events. Research has also been focusing on out-of-the-box therapies including fecal microbiota transplant for UC, dietary interventions for IBD, and allogenic mesenchymal stem cells for perianal fistulizing CD.

With these new therapies, are we modifying disease history and avoiding surgery? The answer seems to be "yes." Edward L. Barnes, MD, and colleagues (Abstract 708) used an insurance dataset to show that the rate of colectomy for UC was reduced significantly between 2007 and 2016. This may be attributable to biologic therapy, change in practice guidelines, awareness of complications such as *C. difficile*, and enhanced disease monitoring. Surgery should not be viewed as a failure – a limited ileocecal resection is more cost effective with equal or better quality of life at 1 year, compared with infliximab therapy, per the randomized LiRIC trial (Lancet Gastroenterol Hepatol. 2017;2:785-92).

Dr. Mahadevan is professor of medicine, University of California at San Francisco Center for Colitis and Crohn's Disease. She has disclosed receiving grant/research support from Celgene, Genentech, Pfizer, and Tigenix, and consulting for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Lilly.

Microbiome – Impact on health and disease

BY GARY D. WU, MD

The gut microbiota influences our biology through our mucosal immune system as well as by leading to the production of bioactive small molecules. I'll describe how gut microbiota influences colon cancer, liver disease, the production of bioactive compounds, as well as the current status and future prospects of microbiota therapeutics.

The gut microbiota may be a factor in colon cancer. Studies have shown that bacterial biofilms are associated with right-sided colon cancers in humans. More recently, a study has shown that mucosal biofilm formation is carcinogenic in an animal model, suggesting that such biofilms may play a role in the disease pathogenesis. From the standpoint of the liver, the microbiome may be a biomarker for diseases such as cirrhosis and fibrosis in patients with nonalcoholic steatohepatitis. Therapeutically, a recent study suggests that the function of gut microbiota can be altered by introducing an engineered *Escherichia coli* bacterial strain to treat hyperammonemia by modifying its metabolism to overproduce arginine, thereby sequestering ammonia produced by gut bacteria into the amino acids (Sci Transl Med. 2019 Jan 16;11[475]. doi: 10.1126/scitranslmed.aau7975). Drug metabolism also can be influenced by the gut microbiota and vice versa. For example, drugs such as metformin have effects on the composition of the gut microbiota in humans. In turn, the gut microbiota and its metabolites can have an influence on hepatic drug metabolism, thereby altering xenobiotic pharmacokinetics and pharmacodynamics.

The production of bioactive small molecules by bacterial metabolism is a topic of intense interest in the microbiome field. Such small molecules have been shown to act as antibiotics, neurotransmitters, immune modulators, and ligands for host receptors. Some of these small metabolites are generated through the dietary aromatic amino acids in which the bacterial enzymatic pathways are being elucidated. Such small molecules have a myriad of functions. For example, indole propionic acid, a bacterial metabolite of tryptophan, can activate the pregnane X receptor to fortify intestinal epithelial barrier function, a pathway that may have relevance to inflammatory bowel disease.


Dr. Wu

Probiotics that are found in dietary supplements represent our currently available strategy for the prevention and/or treatment of disease through the delivery of specific live microbes. However, there are limitations to their effectiveness since none have been approved for the prevention or treatment of any disease process. Via an intensive human subject study, (Cell. 2018 Sep 6;174[6]:1388-405) investigators have shown that the mucosally associated microbiota was a better biomarker for probiotic engraftment than stool was, where the response was very personalized. It's possible that the personalized nature of probiotic engraftment may indicate that "one size may not fit all." There will be a technical review and guideline document published by the American Gastroenterological Association early in 2020.

Currently, the only effective therapeutic modality for the treatment of a human disease by deeply altering the composition of the gut microbiota is the use of fecal microbiota transplantation (FMT) for the treatment of recurrent *Clostridioides difficile* infection (CDI). However, there is now early evidence that FMT might have efficacy in the treatment of a disease other than recurrent CDI, namely ulcerative colitis. Although the short-term risks for FMT are low and quantifiable and long-term risks are largely hypothetical, there is a need for caution and regulation in the practice of FMT. Indeed, long-term engraftment of bacterial strains from the donor into the recipient has been demonstrated. Ultimately, as the science in the microbiota field moves forward together with product development, more sophisticated microbiota-based therapeutics will be generated. During this interim period, the AGA and partner national societies have developed an FMT National Registry to gather information on FMT practice, assess effectiveness as well as short- and long-term safety, and promote scientific investigation.

In conclusion, the field of gut microbiome research is very dynamic and exciting with tremendous opportunities at the intersection between fabulous science and technology, clinical practice, and federal regulation involving the practice of FMT, concurrent with a significant interest in intellectual property and business.

Dr. Wu is the Ferdinand G. Weisbrod Professor in Gastroenterology at the University of Pennsylvania, Philadelphia. He has received research funding from Seres Therapeutics, Intercept Pharmaceuticals, and Takeda; is on the scientific advisory board for Danone and Biocodex; and does consulting for Hitachi High-Technologies.

The changing epidemiology of hepatocellular carcinoma

BY HASHEM B. EL-SERAG, MD, MPH, AGAF

Three main changes characterize the secular trends in the incidence of hepatocellular carcinoma (HCC) in the United States. First, the overall incidence and mortality rates of HCC have been rising for the past 3 decades. Second, Hispanics are disproportionately affected by the HCC increase and have recently surpassed Asian Americans as the group at highest HCC risk. Third, Southern and Western states have registered higher incidence rates of HCC than did the rest of the country.

There are significant racial/ethnic differences in the population distribution of HCC risk factors, notably the disproportionately high prevalence of metabolic syndrome (e.g., obesity, abdominal obesity, and diabetes) and nonalcoholic fatty liver disease (NAFLD) in Hispanics. This observation may explain some of the findings in the secular trends of HCC described above. Most, but not all, studies have reported modest increases in relative risk of HCC in persons with obesity as measured by body mass index.

However, studies investigating more specific obesity measures such as obesity in early adulthood or abdominal obesity reported higher and more consistent HCC risk in Hispanic patients than did those using BMI.

The prevalence of NAFLD in the United States has doubled over the last 2 decades, and is estimated to affect 15%-20% of adults overall, but up to 30% in adult Texas Hispanics. Recently, a large cohort study including 296,707 patients with NAFLD and an equal number of matched controls without NAFLD from 130 facilities of the Department of Veterans Affairs found that patients with NAFLD had several-fold higher HCC risk than controls. The study also reported that HCC incidence rates for patients with NAFLD ranged from 1.6 to 23.7 per 1,000 person-years, with the highest risk among older Hispanic patients with cirrhosis. Approximately 20% of patients with NAFLD and HCC had no evidence of cirrhosis. Lastly, type 2 diabetes, a condition that also is disproportionately higher in Hispanics than in other groups in the United States has been consistently associated with an approximately twofold increase in the risk of HCC.


Dr. El-Serag

Risk factors for cirrhosis and HCC in contemporary clinical practice have shifted from active viral hepatitis to resolved hepatitis C infection or adequately suppressed hepatitis B infection as well as alcoholic liver disease and NAFLD. The shift from uncommon risk factors that carry a considerable increased risk of cirrhosis and HCC (active HCV and HBV) to more common but weaker risk factors (alcohol, NAFLD) is likely to result in a larger pool of chronic liver disease patients at risk for developing cirrhosis and HCC. However, given that the relative risk of HCC is lower with these emerging risk factors, it also will become increasingly difficult to define the highest-risk groups in need of interventions or monitoring. There is a clear need for risk-stratification tools for these patients.

Dr. El-Serag is the Margaret M. and Albert B. Alkek Chair of the department of medicine, Baylor College of Medicine, Houston. He is the President of the AGA Institute. He has no conflicts.

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†Based on a post hoc analysis of 2-week data from 2 previously published identical phase IV, multicenter, randomized, double-blind, placebo-controlled trials that demonstrated efficacy and safety of esomeprazole 20 mg once daily in the morning in subjects with sleep disturbances due to reflux and frequent nighttime heartburn.

‡Complete resolution of heartburn was defined as 7 consecutive days without heartburn.

§First resolution defined as a study day when patients recorded "NO" sleep disturbances due to frequent heartburn on daily diary card.

References: 1. National Sleep Foundation. Ease heartburn at bedtime. https://sleep.org/articles/ease-heartburn-bedtime/. Accessed August 6, 2018. **2.** Johnson DA, Le Moigne A, Hugo V, Nagy P. Rapid resolution of sleep disturbances related to frequent reflux: effect of esomeprazole 20 mg in two randomized, double-blind, controlled trials. *Curr Med Res Opin.* 2015;31(2):243-250.

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