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Courtesy Mount Sinai Health System

Dr. Bruce E. Sands says studies like SEAVUE are important. "We need more head-to-head studies!"

SEAVUE: Biologics go head to head for treating Crohn's

BY WILL PASS

MDedge News

FROM DDW 2021

For biologic-naive adults with moderate to severe Crohn's disease, treatment with adalimumab or ustekinumab leads to similar outcomes, according to results of the head-to-head SEAVUE trial.

When lead author Bruce E. Sands, MD, AGAF, of Icahn School of Medicine at Mount Sinai, New York, compared treatment arms, patients had similar rates of clinical remission at 1 year. All major secondary endpoints, such as endoscopic remission, were comparable, as were safety profiles, Dr. Sands reported at the annual Digestive Disease Week® (DDW).

"From my perspective, this is an important study," Dr. Sands wrote in a virtual chat following his presentation. "We need more head-to-head studies!"

Results from the SEAVUE trial come almost 2 years after Dr. Sands reported findings of another head-to-head IBD trial: VARSITY

See **Biologics** · *page 20*

USPSTF: 45 is the new 50 in CRC screening

BY NEIL OSTERWEIL

The U.S. Preventive Services Task Force (USPSTF) has issued an update of its 2016 recommendations for colorectal cancer screening (JAMA. 2021;325[19]:1965-77), for the first time advising that screening for all average-risk adults begin at age 45. This new recommendation is in line with the guidelines issued by the American Cancer Society, which were updated in 2018 (CA Cancer J Clin. 2018 Jul;68[4]:250-81), to reflect the inescapable truth that CRC is increasingly being diagnosed at a younger age.

Not to be left out, the U.S. Multi-Society Task Force (MSTF) – which represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy – issued a statement supporting lowering the age of initial screening in normal-risk adults to 45, and promised that an update of the 2017 guidelines would include the new recommendation.

Recommendations influence reimbursement

Guidelines are often honored as much in the breach as in the observance, but those issued by the USPSTF have unique

See **USPSTF** · *page 17*

Commentary

The Mediterranean diet gets a green boost for patients with NAFLD

BY WILLIAM F. BALISTRERI, MD

Those of us treating nonalcoholic fatty liver disease (NAFLD) often find ourselves having similar conversations with our patients. After diagnosis, our next step is usually describing to them how they can improve their outcomes through a healthy diet and exercise.

We can point to the latest

See **NAFLD** · *page 16*

INSIDE

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LETTER FROM THE EDITOR

A new world awaits us all

July is typically the month when new students/physicians arrive at academic medical centers, schools, and hospitals to begin the next phase of training. July also marks the beginning of practice for graduating fellows. In the post-COVID world, these settings will have changed dramatically from the past.

Community practices are consolidating rapidly, with many being acquired by private-equity firms, hospitals, and health systems. Private equity made its first investment in GI in 2016, when Audax acquired Miami-based Gastro Health. It was announced this past May that Audax sold Gastro Health to Omers (a larger, Canadian PE firm), marking the first PE sale of a practice (second bite) (Newitt P. "Gastro Health sold to private equity company." Becker's GI & Endoscopy. 2021 May 19). The financial success of this model has not been lost on any community practice, so expect more such transactions.

Health systems are bouncing back from 2020, with balance sheets that are recovering quickly. But operating margins are still narrow so physician productivity is being pushed and burnout is a hot-button issue. Older workers are retiring at increasing rates, and low-wage workers are often reluctant to return to the workforce. Both trends increase Medicare and Medicaid rolls. As more patients enter government insurance programs, provider reimbursement falls. "Manage to Medicare" (bringing costs down to levels that are sustainable on Medicare rates) has again become a common goal. The historic reaction to these financial pressures has been to push commercial rates higher thru market consolidation and emphasize margin-producing services.

Dr. Allen

Health systems are bouncing back from 2020, with balance sheets that are recovering quickly. But operating margins are still narrow.

COVID has changed medicine. We will deliver care differently, and health inequities inherent in the current system will not be tolerable. We now can analyze population-level health outcomes by mining data from enormous databases containing both administrative and health records. Imagine the information we could derive by analyzing inflammatory bowel disease populations scattered across multiple states, all cared for by 1,000 gastroenterologists working in a mega practice that uses a single electronic medical record. That might break down the town-gown barrier quickly.

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

Top cases

Physicians with difficult patient scenarios regularly bring their questions to the AGA Community (https://community.gastro.org) to seek advice from colleagues about therapy and disease management options, best practices, and diagnoses. Here's a preview of a recent popular clinical discussion:

Rafael Ching Companioni, MD, wrote the following in the post "Malnutrition, elevated liver enzymes, anemia, and malabsorption":

"Early 30-year-old female who was initially referred to GI in December 2020 for abnormal liver enzymes ALT 263, AST 114, alk phosp 212, albumin 3.2, bili [within normal limits]. At that time, she reports some diarrhea, few episodes of diarrhea per day, diffuse abdominal pain, ~20 lbs weight loss. She denied herbal medications, OTC medications or other medications. Last travel was 2 years ago to England. No history of anorexia nervosa or bulimia. On examination, cachexia and extremity edema. She has iron deficiency anemia and reactive thrombocytosis. Her initial lipid panel in November 2020, the lipid panel shows total cholesterol 208, LDL 113, triglycerides 227.

"She is still losing weight: 20 lbs from Feb 2021. The liver enzymes elevation resolved. She has anemia, malnutrition and malabsorption. I recommended gluten free diet, MVI, iron pills, protein bars. I had ordered scleroderma work-up and SIBO tests today. I am planning to do MRE."

aga community

See how AGA members responded, and join the discussion: https://community.gastro.org/posts/24416.

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Size, location may help reveal SMICs

BY JIM KLING
MDedge News

Granularly mixed laterally spreading colorectal tumors (GM-LSTs) that are located in the rectum or are larger than 4 cm should be considered to be at high risk of developing into covert submucosal invasive cancer (SMIC), and should be treated by en bloc resection, according to a retrospective analysis of patients from seven Italian centers.

GM-LSTs are 1-cm or larger nonpolypoid lesions with lateral growth. They make up 1%-6% of colorectal lesions, and are important clinically because of the possibility that they are SMICs that aren't visibly apparent.

On the one hand, homogeneous granular-type LSTs have been found to have a very low SMIC risk (0.5%) and are candidates for piecemeal removal, while nongranular LSTs present higher risk, suggesting that en bloc resection would be an appropriate strategy. Piecemeal attempts that discover a SMIC can lead to follow-up surgery because it may not be possible to evaluate submucosal invasion at pathology. Further surgery can be particularly onerous in rectal lesions, where it can reduce quality of life.

On the other hand, granularly mixed LSTs present a conundrum: SMIC risk falls somewhere between the granular and nongranular LSTs, and they make up about 25% of laterally spreading tumors.

Granularly mixed LSTs present a conundrum: SMIC risk falls somewhere between the granular and nongranular LSTs, and they make up about 25% of laterally spreading tumors.

A deeper look

To better characterize GM-LSTs and predict which might be covert SMICs, Ferdinando D'Amico at Humanitas University in Milan and colleagues analyzed data from 693 patients with colorectal GM-LSTs at seven Italian centers, between 2016 and 2019. The results appeared in Clinical Gastroenterology and Hepatology. Median age was 69 years, and 50.6% of patients were men.

Of patients in the study, 9.5% were found to have SMICs at histology. Of these, 62.1% occurred in lesions 4 cm or larger, and none in lesions smaller than 2 cm, and 63.6% occurred in the rectum. Overall, 24.2% of patients underwent en bloc resection.

A multivariate analysis found that lesion size was associated with risk of covert SMIC (odds ratio per mm, 1.02; 95% confidence interval, 1.0-1.03). A cutoff of 4.0 cm yielded the

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Novel oncogene found in hepatoblastoma

BY JIM KLING
MDedge News

A novel oncogene may be a key driver in hepatoblastoma, according to a new study. Hepatoblastoma is the most common form of pediatric cancer, and many tumors harbor beta-catenin mutations and alterations to the Hippo tumor suppression pathway.

In mice, cells can be turned cancerous by coexpressing beta-catenin mutants and the Hippo effector YAP. Some hepatoblastomas have mutations in NFE2L2/NRF2 (NFE2L2), which is a transcription factor that can either promote or suppress tumorigenesis.

In a report in Cellular and Molecular Gastroenterology and Hepatology (2021:12[1]:199-228), researchers led by Huabo Wang, PhD, of the UPMC Children's Hospital of Pittsburgh investigated the potential role of NFE2L2 by expressing all combinations of mutant beta-catenin, YAP^{S127A}, and two NFE2L2 mutants previously discovered in patients (L30P and R34P).

The researchers found that both the L30P and R34P mutations led to an increase in cellular growth and to both necrosis and cyst formation, which are both clinically uncommon. Any two of beta-catenin, YAP^{S127A}, and L30P/R34P caused tumor formation, indicating that NFE2L2 is an on-

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A substantial number of patients with hepatoblastoma are faced with aggressive tumors characterized by multiple nodules at diagnosis, metastases, vascular invasion, chemoresistance, and relapse. In contrast to hepatocellular carcinoma, hepatoblastoma has a low rate of genetic mutations, mainly in two genes CTNNB1 (beta-catenin) and NFE2L2/NRF2. Although only 5%-10% of patients with hepatoblastoma harbor mutations in the NFE2L2/NRF2 gene, the mutations strongly correlate with clinical features of aggressive hepatoblastoma.


Dr. Timchenko

Until today, the role of mutations of the NFE2L2/NRF2 gene in hepatoblastoma was unknown, which raised a question of whether the mutant NFE2L2/NRF2 is really an oncogene. This report by Dr. Wang's group provides clear evidence that two patient-derived NFE2L2/NRF2 mutations, L30P and R34P, are critical for development of aggressive features of hepatoblastoma such as necrosis and cyst formation. Importantly, both L30P and R34P mutations significantly shortened survival of the mice, which correlates with high mortality of patients who have the NFE2L2/NRF2 mutations. It is also important that the authors found copy number variations and missense mutations in the NFE2L2/NRF2 gene by analyzing existing datasets, which emphasizes the role of NFE2L2/NRF2 mutations in aggressive hepatoblastoma.

In summary, this elegant work identified the critical role of the NFE2L2/NRF2 mutations in development of aggressive features of pediatric liver cancers such as low survival rate, fast progression of tumors, and promotion of widespread necrosis. This study also opens new directions which should address a) the combinatory effects of genetic mutations; b) the mechanisms that increase expression of the mutant oncogenes; and c) protein modifications that convert tumor suppressors into new oncogenes.

Nikolai A. Timchenko, PhD, is professor of surgery and director of the liver tumor biology program at Cincinnati Children's Hospital Medical Center. He has no conflicts of interest, but is supported by the Internal Development Funds from CCHMC and by Fibrolamellar Cancer Foundation (FCF-0015).

Continued from previous page

optimal discrimination for SMIC risk, with a 6.0% risk below that size and 14.8% above (OR, 2.32; $P = .002$). The researchers also considered GM-LST location in this multivariate analysis, and found a greater risk of SMIC in those located in the rectum than for those in other colonic segments (15.1% vs. 5.8%; OR, 3.08; $P = .004$). A logistic regression model combining size and location yielded a sensitivity of 47.0%, specificity 82.6%, and area under the curve of 0.69.

When lesions of 4 cm or greater in the rectal area were compared with nonrectal lesions less than 4 cm, the number needed to treat (NNT) to detect one covert SMIC dropped from 20 to 5.

"The 22% risk of covert SMIC for ≥4-cm rectal GM-LSTs equals the 21.4% previously reported as the highest risk for nongranular LSTs, justifying the need for an aggressive treatment, especially when considering that the unexpected finding of a covert SMIC after piecemeal resection of a rectal lesion may result in an unnecessary surgery, with major consequences for the patient. Thus, referral of these patients to a center with adequate competence in advanced resection, including [endoscopic submucosal dissection], should be recommended," the authors wrote.

They noted that the NNT of 5 is low enough to compensate for the risk of conducting ESD instead of piecemeal endoscopic mucosal resection. Meanwhile, the NNT of 20 for smaller, nonrectal tumors puts them close to the risk category of homogeneous granular LSTs, which wouldn't justify a more complex procedure and could instead be resected piecemeal.

For rectal lesions less than 4 cm or nonrectal lesions 4 cm or larger, SMIC risk is below 10%. In deciding which approach to take, endoscopists must weigh the low risk of surgery after discovery of an unexpected SMIC. The authors suggest use of dye or virtual chromoendoscopy for lesion characterization, along with optical magnification if available.

The study had some limitations. One is that the authors did not assess how frequently the SMIC was limited to the dominant nodule, which might affect resection strategies. Another is that the actual SMIC rate in GM-LSTs may have been underestimated: Not only were signs of overt invasion an exclusion criterion, but also patients with difficult-to-treat SMIC lesions might have been referred elsewhere.

The authors disclosed no funding source and declared that they had no relevant financial disclosures.

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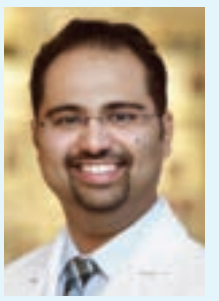
Paris classification, Kudo pit pattern, NICE classification, oh my! Oftentimes, we struggle to make the best decision for our patients when facing a large complex polyp. Choosing between options such as endoscopic mucosal resection or endoscopic submucosal dissection or sending the patient to our surgical colleagues are thoughts that run through our heads. A great deal of research has already been done to subclassify polyps based on several surface characteristics (Kudo) and morphology (Paris) in an attempt to correlate them histologically with the presence of cancer and more importantly the depth of invasion. These two aspects often dictate a much more aggressive approach to patient care. Unfortunately, in spite of great correlation results, our adoption of these classifications and pit patterns into mainstream colonoscopy reporting and care has been lacking; mainly because of the complexity.


Dr. Agarwal

This study by D'Amico and colleagues aims to help give simpler guidance on the risks of laterally spreading tumors based on location and size. Their research revealed that lesions greater than 4 cm and those found in the rectum have a higher chance of having submucosal involvement and thereby necessitate surgery. More importantly, it also gives us insight on what we can tell our patients for lesions in other locations and of different sizes with regard to the outcomes that can be achieved from an endoscopic approach.

Suneal Agarwal, MD, FACG, is assistant professor of gastroenterology and hepatology at Baylor College of Medicine, Houston. He has no conflicts of interest.

Thermal ablation may reduce residual adenomas

BY JIM KLING
MDedge News

Thermal ablation of the defect margin after endoscopic mucosal resection (EMR-T) is associated with reduced recurrence in the treatment of large (≥20-mm) nonpedunculated colorectal polyps (LNPCPs), according to a prospective international cohort study.

Residual or recurrent adenomas (RRAs) are found during 15%-20% of first surveillance endoscopies. EMR-T was previously shown in a randomized trial to be effective at reducing adenoma recurrence during surveillance endoscopy (relative risk, 0.3; $P < .01$).

The U.S. Multi-Society Task Force currently recommends EMR-T for LNPCPs (Gastroenterology. 2020;58:1095-129), but real-world effectiveness remains unknown, wrote Mayenaaz Sidhu, MBBS, of the department of gastroenterology and hepatology at Westmead Hospital in Sydney and colleagues in Gastroenterology (2021 Mar. doi: 10.1053/j.gastro.2021.03.044). Therefore, they undertook an international, multicenter, prospective trial to evaluate the technique in the real world.

The researchers analyzed data from consecutive patients who were referred for treatment of LNPCPs at six tertiary centers. Between May 2016 and August 2020, the study included 1,049 LNPCPs from 1,049 patients. The mean age was 67.3 years, and the median lesion size was 35 mm. Of LNPCPs, 58.7% were tubulovillous adenomas. EMR was technically successful in 98.9%

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This prospective multicenter study "seals" it: Margin ablation should be the standard of care following endoscopic resection of large nonpedunculated colorectal polyps! The study results are impressive with an intention-to-treat recurrence rate of 3%, and only 1.4% if complete margin ablation is achieved!

Dr. Pohl

The results surpass those of the randomized controlled trial from the same group (5% recurrence). According to the authors, refinement in using snare-tip soft coagulation and ensuring a 2- to 3-mm wide ablation margin likely contributed to these outcomes. It should be noted that each of the 17 participating endoscopists underwent ablation training sessions overseen by the senior author. Although the technique might be easy to learn, the learning curve is unclear. The recurrence rate among endoscopists ranged from 0% to 11%, although the number is too low to make any firm conclusions.

Nevertheless, it appears that the two major obstacles of endoscopic large-polyp resection have now been addressed. Clip closure reduces postprocedure bleeding by approximately 50%, and margin ablation minimizes the risk of recurrence! What does it mean for us practicing large-polyp resection? We need to select the right method for the right lesion, apply effective means to remove residual polyp, ablate the margin, and close a defect. Other methods may evolve that can also achieve an effective resection, but for now margin ablation with snare-tip soft coagulation is effective and should be an integral part.

Heiko Pohl, MD, MPH, is professor of medicine at the Geisel School of Medicine at Dartmouth, Hanover, N.H. He reports receiving research grants from Cosmo Pharmaceuticals and from Steris.

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cogene, according to the authors.

Among tumors with changes in all three regions, unbiased RNA sequencing across all combinations of mutations revealed 22 RNA transcripts common to all of them. These are probably the most important contributors to cell transformation and may also be related to increased growth, cystogenesis, and necrosis found in these tumors. Of those transcripts, 10 were highly correlated with survival in human hepatoblastomas, and 17 correlated with survival in more than one adult cancer.

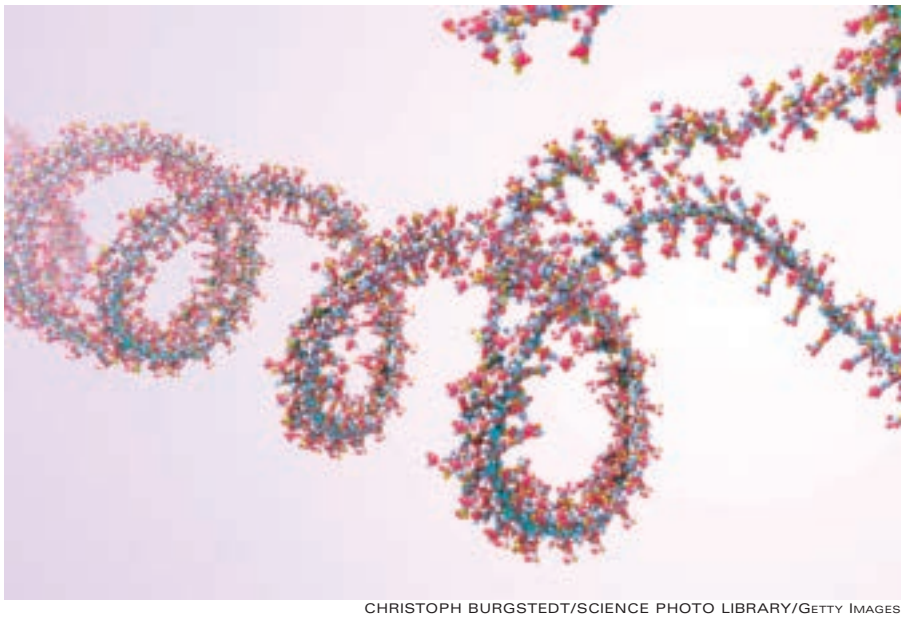
Some hepatoblastomas have mutations in NFE2L2/NRF2 (NFE2L2), which is a transcription factor that can either promote or suppress tumorigenesis.

Although hepatoblastomas have fewer mutations than most tumors, around 5%-10% have mutations in NFE2L2. About half have an increase in the copy number of NFE2L2.

The results suggest that wild-type NFE2L2 could play a role in suppressing cell proliferation in response to oxidative, metabolic, and electrophilic stresses. But the picture is even more complex than that because NFE2L2's pathway can have opposite effects, depending on the timing and context. Early in the oncogenesis pathway, it may protect against the damaging effects of reactive oxygen species. Later, however, it can make cells more tolerant to the effects of oncoproteins and promote tumor evolution, expansion, and even resistance to therapy.

Previous in vitro and tumor xenograft studies had suggested that NFE2L2 targets might play a role in apoptosis, metabolism, angiogenesis, and chemotherapeutic drug detoxification. The new results show that the L30P/R34P mutations can accelerate tumorigenesis caused by beta-catenin mutations and can promote transformation when co-expressed with either beta-catenin or YAP^{S127A}. That suggests that some hepatoblastomas may be driven at least in part by changes to NFE2L2. The researchers speculate that it may also be involved in combination with other oncoproteins in other types of tumors.

The researchers noted that the cysts seen in tumors with NFE2L2 mutations are bloodless, and resembled cysts that are sometimes seen in human hepatoblastomas. They were unrelated to tumor growth rate.



CHRISTOPH BURGSTEDT/SCIENCE PHOTO LIBRARY/GETTY IMAGES

"Our findings demonstrate that NFE2L2 mutants alter redox balance in beta-catenin/YAP^{S127A} [hepatoblastomas] and increase growth, cystogenesis, and necrosis. The unanticipated oncogenicity of L30P/R34P when coexpressed with beta-catenin or YAP^{S127A} also demonstrated their direct role in transformation in vivo and unequivocally established NFE2L2 as an oncoprotein that can be activated by mutation, overexpression, or other factors that perturb the normal NFE2L2:KEAP1 balance," the authors wrote.

The study received funding from various nonindustry sources. The study authors disclosed no conflicts of interest.

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of cases. Overall, 19.1% of cases required an auxiliary modality to completely remove polypoid tissue; most often this was cold avulsion with adjuvant snare-tip soft coagulation (44.4%).

Complete EMR-T was achieved in 95.4% cases. Reasons for failure included extensive post-EMR defect (n = 29), unstable colonoscope position or difficult access (n = 14), and intraprocedural adverse events (n = 5).

Hiroshi Watanabe/Getty Images

Of 803 patients eligible for surveillance colonoscopy, 94% underwent the procedure at a median interval of 6 months. Overall, RRAs were found in 3% of cases. Among lesions with complete EMR-T, 1.4% (10 of 707) had RRAs at first surveillance colonoscopy versus 27.1% (13 of 48) with incomplete EMR-T ($P < .001$). In cases with incomplete EMR-T, lesions were larger (median size, 42.50 mm vs. 37.60 mm; $P = .03$), there was longer procedure time (mean, 60.2 vs. 35.0 minutes; $P = .01$), and there was a greater likelihood of referral for surgery (8.3% vs. 3.0%; $P = .04$).

Intraprocedural bleeding occurred in 6% of cases, and endoscopic hemostasis was achieved in all. Clinically significant post-EMR bleeding occurred in 6.8% of cases, 59.2% of which were managed conservatively, and the remainder were evaluated endoscopically. Bleeding was controlled in every case.

"These findings clearly support and exceed those of a recent randomized trial for EMR-T in the colorectum."

Unlike RRA risk scores that use size, morphology, site, and access score, EMR-T can be used proactively to reduce RRA frequency. It is believed to work by thermally ablating microscopic tissue at the margin. The adverse events reported in the current study were similar to a systematic review and meta-analysis (Gut. 2016 May;65[5]:806-20).

"These findings clearly support and exceed those of a recent randomized trial for EMR-T in the colorectum. They likely reflect refinements in the performance of EMR-T over time, due to greater technical experience and enhanced confidence in its safety. At its inception, the approach to EMR-T may have been timid, however, as experience grew and the safety of EMR-T became evident, a meticulous approach to uniform and complete thermal ablation of the defect margin became the standard of care," the authors wrote.

They added that EMR-T has been shown to benefit in complex LNPCPs, including those that have undergone previous excision attempts and those involving the anorectal junction. The procedure has no added cost, since many endoscopists can readily use snare-tip soft coagulation to manage bleeding events.

"Thermal ablation of the defect margin should be viewed as an essential component of high-quality EMR for LNPCPs, consistent with recent recommendations by the U.S. Multi-Society Task Force on Colorectal Cancer," the authors wrote.

The study was funded by the Cancer Institute of New South Wales, the Gallipoli Medical Research Foundation, and the University of British Columbia. One author reported research support for Olympus, Cook Medical, and Boston Scientific, but the remaining authors disclosed no conflicts.

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Career-spanning strategies to overcome gender bias

BY AMY KARON
MDedge News

The gender gap in gastroenterology persists – currently, women constitute 39% of fellows, but only 22% of senior AGA members and less than 18% of all practicing gastroenterologists – and it has gained even greater significance within the "current historical moment" of the COVID pandemic and growing cognizance of systemic sexism and racism, according to experts.

During the pandemic, women have been more likely to stay home to care for ill family members and children affected by school closures, which increases their already disproportionate share of unpaid work (Lancet. 2020 Jul;396[10244]:80-1), wrote Jessica Bernica, MD, of Baylor College of Medicine in Houston with her associates in Techniques and Innovations in Gastrointestinal Endoscopy (2021. doi: 10.1016/j.tige.2020.12.006). They noted that, according to one study (Proc Natl Acad Sci USA. 2020 Jul;117[27]:15378-81), this "holds true for female physicians, who despite their more privileged positions, also experience higher demands at home, impacting their ability to contribute to teaching, service, and research."

At the same time, the pandemic has brought into focus which jobs are "truly essential" – and that they are "overwhelmingly [held] by women and people of color, who are often underpaid and undervalued," the experts wrote. The growing focus on systemic racism has also increased awareness of the chronic gender discrimination faced by female minorities, as well as by women in general, they added. In the field of gastroenterology, inherent gender bias – both systemic and self-directed – can bar women from advancing beginning as early as medical school.

To help address these issues, the experts outlined key opportunities for change as women navigate professional "forks in the road" throughout their careers.

Throughout their careers

During medical school and residency, women can specifically request gastroenterology rotations ("ideally with both inpatient and outpatient exposure"), attend society conferences, participate in research themselves, and join a research track or serve as chief medical resident. When applying for gastroenterology fellowships, they can prioritize programs with female faculty, which were recently found to be more likely to hire female fellows (Gastroenterology. 2020 May. doi: 10.1016/S0016-5085[20]31344-5).

During fellowship, women can avail themselves of female mentors, who can help them strategize about ways to address gender bias, connect with GI groups and societies, and learn endoscopy techniques, including "unique approaches [that] overcome the challenges of standard scope sizes and accessibility." At the institutional level, opportunities to effect positive changes for women trainees include "formal education on the benefits of hands-on learning and encouraging explicit and open communication between parties regarding invitation to, comfort with, and type of physical contact prior to a case."

After fellowship, early-career gastroenterologists should scrutinize contracts for details on pay and research support, and they should ideally join a practice that either already has many women physicians on staff, or that ensures salary transparency and has "parental leave policies that are compatible with [applicants'] personal and professional goals." But the experts advocated caution about part-time positions, which may purport to offer more flexibility but turn into full-time work for part-time pay and can preclude participation in practice management opportunities.

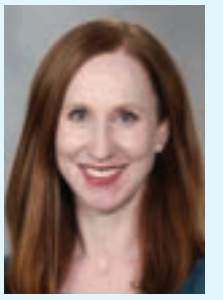
The experts recommended mid-career female gastroenterologists call out their own achievements rather than waiting for recognition, "actively seek promotion and tenure," negotiate their salaries (as men tend to do routinely), and think twice before accepting professional roles that are uncompensated or do not clearly promote career advancement.

Senior gastroenterologists have unique opportunities to spearhead changes in institutional policies and practices, according to the experts. Specific examples include "explicitly stating [in job listings] that salary is negotiable, creating transparent written compensation plans, and conducting audits of job offers" to help mitigate any inequities in pay or hiring practices. In addition, senior women gastroenterologists can mentor individual women in the field, implement formal trainings on implicit bias, ensure that their practice or department tracks the gender of gastroenterologists who join, leave, or are promoted.

The experts did not report receiving funding for the work. They reported having no conflicts of interest.

SDI Productions/Getty Images

Gastroenterology is a male-dominated field; women represent only 18% of current practicing gastroenterologists. Fortunately more women are entering medicine, including our field of gastroenterology, with current statistics showing that 39% of fellows are women. There have been historical barriers to women's entry into the gastroenterology field, but thanks to the efforts of great female leaders in gastroenterology and men who are allies of women in our field, we have seen some of these barriers start to weaken. However, there is much work yet to be done. In fact, many would argue our work is just beginning.



Dr. Raffals

Bernica and colleagues present a thought-provoking piece outlining opportunities for women to navigate their careers and overcome obstacles so that they can achieve professional and personal fulfillment. Spanning the entirety of a women's career, these suggestions highlight the importance of seeking out other women for mentorship and sponsorship and taking advantage of resources available through the various national societies.

In addition to seeking out women for support throughout our careers, we should not overlook the opportunity to seek out our men colleagues who are ready to serve as our allies. In a male-dominated field, our "he-for-she" colleagues are often our greatest allies and sponsors.

Hopefully we will all learn something from Bernica and colleagues' important piece and continue to sponsor and encourage women to practice this great field so that someday our workforce will look more like the patients we are caring for.

Laura E. Raffals, MD, is with the department of gastroenterology and hepatology at Mayo Clinic, Rochester, Minn. She has no conflicts of interest.

ginews@gastro.org

The gift you should be talking about

If you want to make a lasting impact at the AGA Research Foundation, one of the easiest ways is to name us as a beneficiary of one of your assets, such as your retirement plan, life insurance policy, bank account, or donor-advised fund.

When you do, don't forget to notify us of your decisions. Many charities and individuals aren't aware that they have been named to receive a gift. Informing them helps preserve your intentions and ensures that your beneficiaries are able to follow your wishes.

Steps to protect the people and charities you love

- Review your beneficiary designations periodically because circumstances change throughout your lifetime.
- Alert your beneficiaries that you have a life insurance policy or have named them as beneficiaries of a retirement plan.
- Share the location and details of the policy or plan with your beneficiaries.

As you update your beneficiary designations, consider making a gift of a life insurance policy or retirement plan to the AGA Research Foundation so that we can continue to progress with our mission. Then let us know about your decision so that we can carry out your wishes as intended and thank you for your gift.

We want to hear from you

If you have already named the AGA Research Foundation as a beneficiary of a life insurance policy or retirement plan assets, please contact us at foundation@gastro.org today. If you are still creating your estate plan, we would be happy to answer any questions you may have about making this type of gift.

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AGA, GI societies support lowering CRC screening age

American Gastroenterological Association, American College of Gastroenterology, and American Society for Gastrointestinal Endoscopy issued a statement of support that also notes our Multi-Society Task Force on Colorectal Cancer is finalizing our own recommendation to start screening at 45 years of age as well. The U.S. Preventive Services Task Force has made a similar move recently (see p. 1).

Incoming AGA President John M. Inadomi, MD, AGAF, notes that, "We expect this important change to save lives and improve the health of the U.S. population."

AGA fully supports the decision of the USPSTF to reduce the age at which to initiate screening among individuals at average risk for development of colorectal cancer to 45 years. This decision harmonizes the recommendations between the major U.S. screening guidelines including the American Cancer Society and American College of Physicians.

"The analysis by the USPSTF is timely and incredibly helpful to population health and to gastroenterologists and other providers," says Bishr Omary, MD, PhD, AGAF, president of AGA. "We now have clear guidance to start colorectal cancer screening at age 45 for those with average risk and discontinue screening after age 85."

The 2021-2022 research awards cycle is now open

We are pleased to announce that the AGA Research Foundation's research awards cycle is now open. The cycle begins with our two specialty awards focused on digestive and gastric cancers – applications are due on July 21.

AGA–Caroline Craig Augustyn & Damian Augustyn Award in Digestive Cancer: One $40,000 award supports an early-career investigator who holds a career development award devoted to digestive cancer research.

AGA–R. Robert & Sally Funderburg Research Award in Gastric Cancer One $100,000 award supports an established investigator working on novel approaches in gastric cancer research.

In addition to our usual awards portfolio focused on a broad range of digestive diseases, we have established several new awards that will fund research focused on health and health care disparities, including those listed below. More information is available online at https://gastro.org/research-and-awards.

- Pilot Research Awards: Currently accepting applications
- Research Scholar Awards: Open Aug. 12
- AGA–Aman Armaan Ahmed Family Summer Undergraduate Research Fellowship: Open Oct. 6.

Get to know this year's Julius Friedenwald Medal recipient

In last month's Gastroenterology, Vijay H. Shah, MD, AGAF, and colleagues shared a commentary on the esteemed career of this year's Julius Friedenwald Medal recipient, Michael Camilleri, MD, AGAF, of the Mayo Clinic in Rochester, Minn. Here are some fun facts about this year's honoree:

- While growing up in Malta, he was influenced by a combination of his uncle, who was a kindly family physician, and by watching medical dramas (specifically, Dr. Kildare and Marcus Welby, M.D.) on his family's black-and-white television set during his childhood. These experiences led Dr. Camilleri to commit to a career in medicine by the age of 8.
- Dr. Camilleri started his long journey at the Mayo Clinic as a research fellow in 1983 by conducting fundamental clinical research in GI motility.
- With 660 peer-reviewed original articles and 290 published invited reviews and editorial publications, Dr. Camilleri has redefined the understanding and treatment of disorders covering the entire GI tract from rumination syndrome to pelvic dyssynergia.
- Dr. Camilleri has mentored 79 postdoctoral fellows since he became a member of the faculty at Mayo Clinic 35 years ago.

Dr. Michael Camilleri

Read more about Dr. Camilleri's life and contributions to the GI community in a commentary appearing in the June issue of Gastroenterology (2021 Jun. https://doi.org/10.1053/j.gastro.2021.04.039), which was written by his colleagues and friends, including Dr. Shah and Adil E. Bharucha, MBBS, MD, AGAF; David A. Katzka, MD, AGAF; and Gregory J. Gores, MD, AGAF.

Sporebiotics improve functional dyspepsia symptoms

BY WILL PASS
MDedge News

FROM DDW 2021

Compared with placebo, sporebiotics significantly reduced postprandial distress, epigastric pain, and several other symptoms of functional dyspepsia, reported lead author Lucas Wauters, MD, PhD, of University Hospitals Leuven (Belgium), and colleagues.

"Acid suppressive or first-line therapy with PPIs [proton pump inhibitors] for functional dyspepsia has limited efficacy and potential long-term side effects," the investigators reported at the annual Digestive Disease Week® (DDW). "Spore-forming bacteria or sporebiotics may be effective for postprandial distress and epigastric pain or burning symptoms, offering benefits which may differ in relation to PPI intake."

Sporebiotics improve various symptoms

To test this hypothesis, the investigators recruited 68 patients with functional dyspepsia who had similar characteristics at baseline. Half of the participants (n = 34) were taking PPIs.


Dr. Wauters

Patients were randomized in a 1:1 ratio to receive 2.5 x 10^9 CFU of *Bacillus coagulans* MY01 and *B. subtilis* MY02 twice daily for 8 weeks, or matching placebo. Following this period, an additional 8-week open-label regimen was instituted, during which time all patients received sporebiotics. Throughout the study, a daily diary was used to self-report symptoms.

The primary outcome, measured at 8 weeks, was clinical response, defined by a decrease in weekly postprandial distress symptoms greater than 0.7 among patients who had a baseline score greater than 1.0. Secondary outcomes included change in postprandial distress symptoms greater than 0.5 (minimal clinical response), as well as changes in cardinal epigastric pain, cardinal postprandial distress, and other symptoms. At baseline and 8 weeks, patients taking PPIs underwent a ^{14}C-glycocolic acid breath test to detect changes in small intestinal bacterial overgrowth.

At 8 weeks, a clinical response was observed in 48% of patients taking sporebiotics, compared with 20% of those in the placebo group (P = .03). At the same time point, 56% of patients in the treatment group had a minimal clinical response versus 27% in the control group (P = .03).

Spore-forming probiotics were also associated with significantly greater improvements in cardinal postprandial distress, cardinal epigastric pain, postprandial fullness, and upper abdominal pain. A trend toward improvement in upper abdominal bloating was also seen (P = .07).

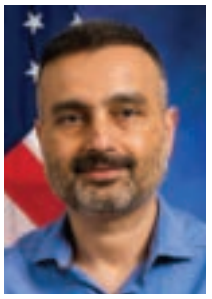
Among patients taking PPIs, baseline rates of positivity for bile acid breath testing were similar between those in the sporebiotic and placebo group, at 18% and 25%, respectively (P = .29). After 8 weeks, however, patients taking spore-forming probiotics had a

Continued on following page

Does MELD need an update?

Time for change

The population with cirrhosis that existed 20 years ago has shifted radically. Patients with cirrhosis currently tend to either be much older with more comorbid conditions that predispose them to chronic kidney disease and cerebrovascular and cardiovascular compromise or be younger with an earlier presentation of alcohol-associated hepatitis. Moreover, the widespread availability of hepatitis C virus eradication has changed the landscape. This is relevant because a recent United Network for Organ Sharing analysis showed that the concordance between MELD score and 90-day mortality was the lowest in the rapidly increasing population with alcohol-related and nonalcoholic fatty liver disease etiologies, but conversely, that concordance was the highest in the population with hepatitis C–related cirrhosis.


Dr. Bajaj

These demographic shifts in age and the changes in etiology likely lessen the predictive power of the current MELD score iteration.

Jasmohan S. Bajaj, MD, AGAF, is with the division of gastroenterology, hepatology, and nutrition at Virginia Commonwealth University, Richmond, and Richmond VA Medical Center. He has no conflicts of interest.

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

Take it slow

MELD relies on a simple set of laboratory values that are easily obtained at any clinical lab and are already being routinely monitored as part of standard care for patients with end-stage liver disease.


Dr. Heimbach

The MELD system initially required just three variables (bilirubin, creatinine, international normalized ratio), and was updated to include just four variables with the adoption of MELD-Na in 2016, which added sodium levels. The MELD- and MELD-Na–based system is a highly reliable, accurate way to rank patients who are most at risk of death in the next 3 months, with a c-statistic of approximately 0.83-0.84. Perhaps the greatest testament to strength of MELD is that, following the adoption of MELD-based liver allocation, the MELD-based system has gradually been adopted as the system of liver allocation by most countries around the world.

Julie K. Heimbach, MD, is a transplant surgeon and the surgical director of liver transplantation at Mayo Clinic in Rochester, Minn. She has no conflicts to report.

Dear colleagues and friends,

The Perspectives series continues! There are few issues in our discipline that are as challenging, and controversial, as liver transplant prioritization. The Model for End-Stage Liver Disease (MELD) has been the mainstay for organ allocation for nearly 2 decades, and there has been vigorous debate as to whether it should remain so. In this issue, Dr. Jasmohan S. Bajaj and Dr. Julie K. Heimbach discuss the strengths and limitations of MELD and provide a vision of upcoming developments. As always, I welcome your feedback and suggestions for future topics at ginews@gastro.org.

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


Dr. Kahi

Continued from previous page

significantly lower rate of bile acid breath test positivity (7% vs. 36%; *P* = .04), suggesting improvements in small intestinal bacterial overgrowth.

In the open-label portion of the trial, patients in the treatment group maintained improvements in postprandial distress. Patients who switched from placebo to sporebiotics had a significant reduction in postprandial distress symptoms.

At 8 weeks, sporebiotics were associated with a trend toward fewer side effects of any kind (16% vs. 33%; *P* = .09), while rates of GI-specific side effects were comparable between groups, at 3% and 15% for sporebiotics and placebo, respectively (*P* = .2).

"Spore-forming probiotics are effective and safe in patients with functional dyspepsia, decreasing both postprandial distress and epigastric pain symptoms," the investigators concluded. "In patients [taking PPIs], sporebiotics decrease the percentage of positive bile acid breath tests, suggesting a reduction of small intestinal bacterial overgrowth."

Results are promising, but big questions remain

Pankaj Jay Pasricha, MBBS, MD, vice chair of medicine innovation and commercialization at Johns Hopkins and director of the Johns Hopkins Center for Neurogastroenterology, Baltimore, called the results "very encouraging."

"This [study] is the first of its kind for this condition," Dr. Pasricha said in an interview. "It will be very interesting to see whether others can reproduce these findings, and whether [these improvements] are sustained beyond the first few weeks or months."

"Spore-forming probiotics are effective and safe in patients with functional dyspepsia, decreasing both postprandial distress and epigastric pain symptoms."

He noted that determining associated mechanisms of action could potentially open up new lines of therapy, and provide greater understanding of pathophysiology, which is currently lacking.

"We don't fully understand the pathophysiology [of functional dyspepsia]," Dr. Pasricha said. "If you don't understand the pathophysiology, then it's difficult to identify the right molecular target to address the root cause. Instead, we use a variety of symptomatic treatments that aren't actually addressing the root cause, but studies like this may help us gain some insight into the cause of the problem, and if it is in fact a fundamental imbalance in the intestinal microbiota, then this would be a rational approach."

It's unclear how sporebiotics may improve functional dyspepsia, Dr. Pasricha noted. He proposed three possible mechanisms: The bacteria could be colonizing the intestine, they could be releasing products as they pass through the intestine that have a therapeutic effect, or they may be altering bile acid metabolism in the colon or having some other effect there.

"It's speculative on my part to say how it works," Dr. Pasricha said. "All the dots remain to be connected. But it's a good start, and an outstanding group of investigators."

Dr. Wauters and colleagues reported no conflicts of interest. Dr. Pasricha disclosed a relationship with Pendulum Therapeutics.

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Will this "green" diet be added to the menu?

NAFLD *from page 1*

data espousing the benefits of moderate weight reduction. The recently released American Gastroenterological Association Clinical Practice Update (Gastroenterology. 2021 Feb;160[3]:912-918) gives us compelling evidence of what can be achieved with specific thresholds of total body weight loss: >5% can decrease hepatic steatosis, >7% potentially leads to resolution of nonalcoholic steatohepatitis, and >10% possibly allows for regression or stability of fibrosis.

The authors suggest that the mechanisms by which polyphenols reduced steatosis and prevented liver injury may include reduced de novo lipogenesis, increased fatty acid oxidation, and reduced oxidative stress.

More often than not, our patients then ask us, "What diet do you recommend?"

The AGA's Clinical Practice Update recommends that people with NAFLD follow the Mediterranean diet, minimize saturated fatty acid intake (specifically red and processed meat), and limit or eliminate consumption of commercially produced fructose.

It's a tried-and-true, evidence-based recommendation. Yet, recent data suggest that modifying the Mediterranean diet so that it's further enriched with specific green polyphenols may yield even more benefits to at-risk patients.

Westend61/Getty Images

The upside of a greener Mediterranean diet

In a recently published study (Gut. 2021 Jan 18. doi: 10.1136/gutjnl-2020-323106), investigators behind the DIRECT-PLUS clinical trial randomly assigned 294 participants with abdominal obesity/dyslipidemia into three diet groups (all accompanied by physical activity): standard healthy dietary guidelines (HDG), standard Mediterranean, and the so-called green Mediterranean diet.

Both Mediterranean diet groups were calorie restricted and called for 28 g/day of walnuts (+440 mg/day polyphenols provided). However, the green Mediterranean diet was further supplemented with 3-4 cups/day of green tea and 100 g/day of Mankai (derived from a *Wolffia globosa* aquatic plant strain) in the form of frozen cubes turned into a green shake that replaced dinner (+1,240 mg/day total polyphenols provided). The percent change in intrahepatic fat content was quantified continuously by proton magnetic resonance spectroscopy. NAFLD was defined as an intrahepatic fat content of >5%.

After 18 months, the prevalence of NAFLD declined to 54.8% in the HDG group, 47.9% in the standard Mediterranean group, and 31.5% in the green Mediterranean group. Both Mediterranean groups achieved similar moderate weight loss and had significantly higher total plasma polyphenol levels versus the HDG group. However, the green Mediterranean group achieved significantly greater proportional intrahepatic fat content loss (–38.9%) than both the standard Mediterranean (–19.6; $P = .023$) and HDG (–12.2%; $P < .001$) groups.

Dr. Balistreri

In isolating the individual components of the diets, researchers determined that the degree of intrahepatic fat content loss was significantly associated with increased Mankai and walnut intake, decreased red/processed meat consumption, improved serum folate and adipokines/lipids biomarkers, and changes in microbiome composition and specific bacteria.

The authors suggest that the mechanisms by which polyphenols reduced steatosis and prevented liver injury may include reduced de novo lipogenesis, increased fatty acid oxidation, and reduced oxidative stress.

In an additional analysis, DIRECT-PLUS investigators also revealed the beneficial effects of the green Mediterranean diet on cardiometabolic health (Heart. 2020 Nov 23. doi: 10.1136/heartjnl-2020-317802). Although both Mediterranean diets achieved similar weight loss (–6.2 kg for green Mediterranean and –5.4 kg for standard Mediterranean), which was superior to that observed in the HDG group (–1.5 kg; $P < .001$), the green Mediterranean group had a greater reduction in waist circumference than the standard Mediterranean group (–8.6 vs. –6.8 cm, respectively; $P = .033$). Within 6 months, the green Mediterranean group also achieved a greater decrease in low-density lipoprotein cholesterol levels, diastolic blood pressure, and insulin resistance.

A new dietary tool for combating obesity

The rising global incidence of NAFLD has made it even more urgent to identify new and improved ways of preventing the onset of obesity-related complications. To aid those efforts, we've been equipped with useful tools for educating our patients and their families, such as the 2020-2025 Dietary Guidelines for Americans from the U.S. Department of Agriculture, which makes a clear case for the disease-combating effects of healthy eating patterns.

This message does not appear to be making the impact it should, however, particularly among teens and young adults. It was recently reported that in 2017 only 7% of U.S. high school students consumed recommended amounts of fruits and only 2% consumed enough vegetables to meet USDA recommendations (MMWR Morb Mortal Wkly Rep. 2021 Jan 22;70[3]:69-74).

Novel approaches, including enhanced school and community programs, will be required to address this issue, but so will presenting patients with satisfactory dietary alternatives. Compellingly, DIRECT-PLUS investigators reported an 89.8% retention rate at 18 months among volunteers, who were able to comply with the dietary regimen with no significant complaints regarding taste. This signals that, even though the "green" modification is more stringent than the typical Mediterranean regimen, it is one to which participants can adhere.

Although the real-world applicability of this diet remains to be seen, DIRECT-PLUS gives us encouraging evidence that a Mediterranean diet amplified with green plant–based proteins/polyphenols can lead to twice the intrahepatic fat loss, as compared to other nutritional strategies, and reduce the rate of NAFLD.

And as we know, having another dietary option to offer our patients is always a welcome addition to the menu.

Iris Shai, PhD, one of the authors of the study, "Effect of green-Mediterranean diet on intrahepatic fat: The DIRECT PLUS randomised controlled trial," is an adviser to Hinoman, which markets Mankai. Ilan Youngster, MD, another author of that study, is medical adviser for Mybiotix.

Dr. Balistreri is with the department of hepatology & nutrition at Cincinnati Children's Hospital Medical Center. He has disclosed no relevant financial relationships.

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New 'minimal monitoring' approach to HCV treatment

BY CALEB RANS, PHARMD
MDedge News

A novel minimal monitoring (MINMON) approach to hepatitis C virus (HCV) treatment was safe and achieved sustained virology response (SVR) compared to current clinical standards in treatment-naive patients without evidence of decompensated cirrhosis, according to a recent study.

"This model may allow for HCV elimination, while minimizing resource use and face-to-face contact," said investigator Sunil S. Solomon, MBBS, PhD, of Johns Hopkins University in Baltimore. "The COVID-19 pandemic has highlighted the urgent need for simple and safe models of HCV [care] delivery."

Dr. Solomon described the new approach to HCV treatment during a presentation at this year's Conference on Retroviruses and Opportunistic Infections virtual meeting.

ACTG A5360 was an international, single-arm, open-label, phase 4 trial that enrolled 400 patients across 38 treatment sites.

The researchers evaluated the efficacy and safety of the MINMON approach in treatment-naive individuals who had no evidence of decompensated cirrhosis. Study participants received a fixed-dose, single-tablet regimen of sofosbuvir 400 mg/velpatasvir 100 mg once daily for 12 weeks.

The MINMON approach had four key elements: no pretreatment genotyping, all tablets dispensed at study entry, no scheduled on-treatment clinic visits/labs, and two remote contacts at weeks 4 (adherence evaluation) and 22 (scheduled SVR visit). Unplanned visits for patients' concerns were permitted.

Key eligibility criteria included active HCV infection (HCV RNA > 1,000 IU/mL) and no prior HCV treatment history. Persons with HIV coinfection (50% or less of sample) and compensated cirrhosis (20% or less of sample) were also eligible. Persons with chronic hepatitis B virus infection and decompensated cirrhosis were excluded.

The primary efficacy endpoint was SVR, defined as HCV RNA less than the lower limit of quantification in the first sample at least 22 weeks post treatment initiation. The primary safety endpoint was any serious adverse events (AEs) occurring between treatment initiation and week 28.

The median age was 47 years, and 35% were female sex at birth. At baseline, 166 (42%) patients had HIV coinfection and 34 (9%) had compensated cirrhosis.

After analysis, the researchers found that remote contact was successful at weeks 4 and 22 for 394 (98.7%) and 335 (84.0%) participants, respectively.

In total, 15 (3.8%) participants recorded 21 unplanned visits, 3 (14.3%) of which were due to AEs, none of which were treatment related. One participant prematurely discontinued therapy for an AE.

HCV RNA data at SVR were available for 396 participants. Overall, 379 patients (95.0%) achieved SVR (95% confidence interval, 92.4%-96.7%).

With respect to safety, serious AEs were reported in 14 (3.5%) participants through week 24 visit, none of which were treatment related or resulted in death.

Dr. Solomon acknowledged that a key limitation of the study was the single-arm design. As a result, there was no direct comparison to standard monitoring practices. In addition, these results may not be generalizable to all nonresearch treatment sites.

"The COVID-19 pandemic has required us to pivot clinical programs to minimize in-person contact, and promote more remote approaches, which is really the essence of the MINMON approach," Dr. Solomon explained.

"There are really wonderful results in the population that was studied, but may reflect a more adherent patient population," said moderator Robert T. Schooley, MD, of the University of California, San Diego.

During a discussion, Dr. Solomon noted that the MINMON approach may be further explored in patients who are actively injecting drugs, as these patients were not well represented in the present study.

Dr. Solomon disclosed financial relationships with Gilead Sciences and Abbott Diagnostics. The study was funded by the National Institutes of Health and Gilead Sciences.

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Multiple options for screening recommended

USPSTF *from page 1*

sway, according to Sonia S. Kupfer, MD, AGAF, of the section of gastroenterology, hepatology, and nutrition at the University of Chicago, and colleagues.

"While other guidelines have recommended this younger age, the USPSTF guidelines directly inform insurance coverage and waiving of cost sharing as part of federal law," they wrote in an editorial accompanying the USPSTF guideline statement in the Journal of the American Medical Association (JAMA Network Open. 2021 May. doi: 10.1001/jamanetworkopen.2021.12593).

Although the USPSTF rated its recommendation on starting at age 45 a "B" level – indicating a moderate certainty of moderate benefit – it's an important step, Dr. Kupfer said in an interview.

"The big advantage here is that we may be able to make a dent in this early-onset colorectal cancer, which, having seen many of these patients, is very alarming, and they don't always seem to have classic risk factors," she said. "So, getting them when we can potentially prevent cancer by taking out polyps, or even getting them in an earlier stage, certainly will be beneficial."

The MSTF also considered recommending 45 as the starting age for normal-risk patients in its 2017 guidelines (Am J Gastroenterol. 2017 Jul;112[7]:1016-30), noted Douglas Rex, MD, AGAF, who was chair of the committee that drew up those guidelines, as well as director of endoscopy at Indiana University Hospital in Indianapolis.

"Since that time there has been more evidence, and there's also some empiric evidence, about the yield of screening in the 45- to 49-year-old age group," he said in an interview.

'The one that gets done'

Although the various guidelines differ in specifics, all are in agreement on the general proposition that colonoscopy is the gold standard for screening and detecting the presence of polyps, adenomas, and CRC.

But as USPSTF member Martha Kubik, PhD, RN, director of the George Mason University School of Nursing in Fairfax, Va., said in a statement: "The right test is the one that gets done."

Gastroenterologists acknowledge that, despite its efficacy, colonoscopy is an invasive procedure involving meticulous and unpleasant and/or uncomfortable bowel prep, sedation, and significant time requirements.

In the theory that something is better than nothing, with clinical evidence of varying degrees of quality, the USPSTF recommends the following procedures or tests for average-risk adults:

- Colonoscopy screening every 10 years.
- Flexible sigmoidoscopy every 10 years plus annual fecal immunochemical test (FIT).
- CT colonography every 5 years.
- High-sensitivity guaiac fecal occult blood test (gFOBT; Hemoccult II) or FIT every year.
- Stool DNA-FIT (Cologuard) every 1-3 years.

The Food and Drug Administration also recently approved an artificial intelligence device designed for use with an endoscope, which its manufacturer says can help clinicians detect gastrointestinal lesions they might otherwise miss. This is not a new screening method, but rather an enhancement of existing ones. It neither diagnoses lesions nor recommends treatments, and is not intended to take the place of laboratory sampling.

"I think artificial intelligence is poised to make colonoscopy more effective," Dr. Rex said. "In the first five trials that we've seen, the average increase in the adenoma detection rate has been 11%, and for each 1% gain in the adenoma detection rate, patients have about a 3% decline in their risk of getting cancer after a colonoscopy and about a 5% decline in their risk for fatal cancer. Those are the largest gains that we've seen from a technology."

Different evidence, varied outcomes

Despite the recommendations, a quick dive into the morass of evidence from multiple studies fea-

Continued on following page

AGA Clinical Practice Update: Expert Review

Chemoprevention for colorectal neoplasia

BY AMY KARON
MDedge News

Experts assessed different chemopreventive agents meant to reduce the incidence of colorectal neoplasia and associated mortality based on whether these agents were effective and safe, but they found few fit both criteria, according to a new American Gastroenterological Association Clinical Practice Update Review.

That said, the update does advise that clinicians use low-dose aspirin therapy in patients who are younger than 70 years with at least a 10-year life expectancy, are not at high risk for bleeding, and have at least a 10% cardiovascular disease risk over the next decade.


Dr. Liang

This best practice advice statement reflects "high-quality trial data" for this patient population and also echoes U.S. Preventive Services Task Force recommendations (Ann Intern Med 2016 Jun;164[12]:836-45), wrote Peter S. Liang, MD, MPH, and his associates on behalf of the American Gastroenterological Association. However, they note that low-dose aspirin therapy has shown inconsistent results for older patients and that its chemopreventive benefits always should be weighed against an individual's bleeding risk.

Published in Clinical Gastroenterology and Hepatology (2021 Feb 10. doi: 10.1016/j.cgh.2021.02.014), the AGA's Clinical Practice Update Review also recommends considering low-dose aspirin therapy for patients with a history of colorectal neoplasia, based on data from several trials in which daily doses of 81-325 mg were associated with a significantly lower likelihood of recurrence of earlier-stage adenomas (the findings did not extend to patients with more advanced lesions). Evidence on sessile serrated polyps is sparser, but there is some indication for a benefit in this setting, the experts noted.

Their best-practice advice also covers nonaspirin nonsteroidal anti-inflammatory drugs, metformin, calcium, vitamin D, folic acid, and statins. Among these agents, only metformin receives even a conditional green light. "Because of the results of a large number of observational studies, a small adenoma trial, as well as a favorable safety profile, metformin may be considered for chemoprevention against colorectal neoplasia in individuals with diabetes," the experts concluded. Support for this best-practice advice includes a meta-analysis of colorectal cancer–specific survival in 17 observational studies (Oncotarget. 2017;8[16]:26448-59), a meta-analysis of colorectal cancer incidence in 14 observational studies (Oncotarget. 2017 Feb;8[9]:16017-26), and a randomized, placebo-controlled trial in which 250 mg daily metformin was safe and associated with a 40% lower risk of recurrent adenoma (Lancet Oncol. 2016 Apr;17[4]:475-83).

For calcium, study findings have been mixed, and a recent large clinical trial found no overall benefit for adenoma prevention (N Engl J Med. 2015; 373[16]:1519-30). Because high-dose calcium has been linked to kidney toxicity, hypercalcemia, and prostate cancer, its risks likely outweigh any benefits, the experts concluded. Vitamin D (as monotherapy or with calcium) also has shown no overall benefit for preventing adenomas or sessile serrated lesions.

NSAIDS are not recommended to prevent colorectal neoplasia among average-risk individuals. Cyclooxygenase-2 inhibitors pose "substantial cardiovascular risks," while nonselective NSAIDs are associated with a significantly increased risk for gastrointestinal bleeding. Meta-analyses have shown no benefit of folic acid for preventing colorectal neoplasia, and observational studies on statins have produced only mixed results.

No funding sources were reported. The experts reported having no conflicts of interest.

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tured in the updated USPSTF guidelines shows that not all screening methods are created equal.

A single colonoscopy, for example, has been shown in large cohort studies to be associated with a 68% reduction in CRC mortality vs. no screening, compared with a 26% reduction with flexible sigmoidoscopy performed every 3-5 years, 22% reduction with Hemoccult II, and 10% with FIT every 2 years.

The USPSTF investigators did not find any studies evaluating the effectiveness of CT colonography, high-sensitivity gFOBT, stool DNA with or without FIT, or serum tests on CRC incidence, CRC mortality, or both. The two visualization methods for which studies were available, colonoscopy and CT colonography, were generally comparable in sensitivity and specificity for detecting and correctly identifying adenomas 6 mm and larger, although colonography had higher sensitivity for CRC than colonoscopy.

When performed in two to nine annual or biennial rounds, gFOBT was associated with a reduction of CRC-specific mortality of 9% after 19.5 years and 22% at 30 years, compared with no screening.

In observational studies, screening colonoscopy and FIT were both associated with lower risk of CRC incidence or mortality, compared with no screening.

When to stop

The major guidelines are all in agreement that once an individual reaches age 75, the decision about whether to continue screening should be made on a case-by-case basis, depending on the patient's overall health, relative risks, and life expectancy.

But if a study published 2 days after the release of the USPSTF guidelines is any indication, just as 45 is the new 50 for starting screening, 85 may be the new 75 for stopping it.

As researchers from Mass General Cancer Center in Boston reported in JAMA Oncology (2021 May. doi: 10.1001/jamaoncol.2021.1364), screening endoscopy for persons older than 75 in otherwise good health can reduce the risk for CRC incidence and CRC-related death by approximately 40%.

The researchers also found, however, that screening did not provide a significant survival benefit for individuals older than 75 with cardiovascular disease, diabetes, or three or more other health conditions.

"Until now, there really weren't clear data to help us decide whether patients should be screened after age 75," coinvestigator Andrew T. Chan, MD, MPH, AGAF, a gastroenterologist and chief of the clinical and translational epidemiology unit at Mass General, said in a statement. "Current guidance was largely based on modeling and extrapolation of studies conducted in other age groups, and not on solid data to show whether screening was actually helpful in an older population."

In an interview, Dr. Chan said that, while the recommendation to screen older adults has to be tailored to individual risk factors, "it should help to provide more confidence for clinicians and patients."

"I think this is particularly important, because we know that the population as a whole is aging, so more and more people are in this category of over the age of 75, and it's not an infrequent issue in the clinic as to what to continue with respect to preventative interventions," he said.

Dr. Kupfer said that the findings by Dr. Chan and colleagues are largely in keeping with guideline recommendations.

"We factor in a lot of different things, including comorbidities, in making the decision to continue screening up to age 85. Certainly, physiological age and chronological age aren't always the same, so not every 75-year-old is going to be in the same boat," she said.

"The risk goes up as people get older, but there starts to be competing mortality at some point, and if you have to do a colonoscopy there are obviously issues related to sedation that, as someone gets older, we have to take into consideration."

Patients frequently confuse screening with surveillance, Dr. Rex said, and he has had patients tell him: "I hear you don't do these anymore on people over the age of 75."

"But that's not true," Dr. Rex emphasized. "Screening is generally considered appropriate even up to the age of 85, but between 75 and 85 it should be considered on an individual basis, and there are several considerations there. ... One is whether a patient has ever been screened before. The second is how they were screened. Third is their life expectancy and how many comorbidities they have. And fourth is their personal feelings about it and interest in it."

He pointed out that the false-positive rate of stool DNA-FIT tests

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increases with age, and that, for older patients who were previously screened, a standard FIT test may be a more appropriate.

So doc, what should I do?

Different screening methods with varying efficacy and multiple guidelines, levels of evidence, individual risk factors – how can clinicians make sense of all these data at the practice level?

"Any modality can be used for screening. Colorectal cancer screening can be done in a number of different ways, and I think that sometimes gets lost in the shuffle, and the thought becomes that everybody has to get a colonoscopy at 45, but there are certainly other tests," Dr. Kupfer said.

"This just reminds us that we should be thinking about ways we can be doing screening on a population basis, so that we make sure there is equity," she said.

It's also important to remember that patients with familial CRC syndromes should begin screening at an even earlier age than average-risk adults, she emphasized.

"To really make a dent in early-onset colorectal cancer, we have to continue to take an active case–finding approach," she said.

Dr. Rex noted that, despite minor differences, the major guidelines are all similar in their initial statements that screening works.

"We've still got 50,000 people a year dying from colorectal cancer, lots more than that of new cases," he said. "If you look at a single factor contributing to that the most, it's that a lot of the American public is not getting screened at all – it can be up to 40% of the population, depending on what state you're in."

Although there are a variety of screening methods available, there are few studies directly comparing them, leaving clinicians at the practice level with the task of presenting all or some of them to patients.

"What the Multi-Society Task Force says that is different, and I think that they get right, is that we don't have any data [indicating] that offering five, six, or seven options increases the chance of screening – there's really no evidence that going past two does," Dr. Rex said.

"The list of options also includes things that nobody actually does," he added. "For example, flexible sigmoidoscopy has dropped off the map, and FIT has largely replaced guaiac-based testing, even high-sensitivity guaiac. Nobody is really doing CT colonography. The three tests that are being used are colonoscopy, FIT, and [stool DNA-FIT]."

Dr. Rex said that he favors sequential offers, with colonoscopy first, emphasizing the benefits for higher-risk patients, and if the patients refuse, offering a fecal-based test.

"Minimizing the number of options makes the conversation feasible, and it's still very responsible," he said.

Dr. Kupfer has performed collaborative research with Myriad Genetic Laboratories. She is an editorial advisory board member for GI & Hepatology News. Dr. Rex serves or served as a consultant for Olympus; Boston Scientific; Medtronic; and Aries; and received research support from Endo-Aid; Olympus; and Medivators. He has ownership in ai4gi. He is an editorial board member for Medscape Gastroenterology. Dr. Chan has served as a consultant to Pfizer, Bayer AG, and Boehringer Ingelheim.

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Rapid onset, robust results seen in both

Biologics *from page 1*

(N Engl J Med. 2019 Sep 26;381[13]:1215-26), which demonstrated the superiority of vedolizumab over adalimumab among patients with moderate to severe ulcerative colitis.

The multicenter, double-blinded SEAVUE trial involved 386 patients with biologic-naive Crohn's disease who had failed corticosteroids or immunomodulators. All patients had Crohn's Disease Activity Index (CDAI) scores ranging from 220 to 450 and had at least one ulcer detected at baseline ileocolonoscopy. Participants were randomized in a 1:1 ratio to receive monotherapy with either subcutaneous adalimumab (citrate-free; 160 mg at baseline, 70 mg at week 2, then 40 mg every 2 weeks) or ustekinumab, which was given first intravenously at a dose of 6 mg/kg then subcutaneously at 90 mg every 8 weeks. The primary endpoint was clinical remission at week 52, defined by a CDAI score less than 150.

Results were statistically similar across all endpoints, with clinical remission at 1 year occurring in 64.9% and 61.0% of patients receiving ustekinumab and adalimumab, respectively (P = .417).

"Both treatments demonstrated rapid onset of action and robust endoscopy results," Dr. Sands noted; he reported comparable rates of endoscopic remission, at 28.5% and 30.7% for ustekinumab and adalimumab, respectively (P = .631).

Among secondary endpoints, ustekinumab demonstrated some superiority, with greater maintenance of clinical response at week 52 among patients with response at week 16 (88.6% vs. 78.0%; P = .016), greater reduction in liquid/soft stools in prior 7 days from baseline to week 52 (–19.9 vs. –16.2; P = .004), and greater reduction in sum number of liquid/soft stools and abdominal pain scores in prior 7 days from baseline to week 52 (–29.6 vs. –25.1; P = .013).

Safety metrics were similar and consistent with previous experience. Although the adalimumab group had a higher rate of discontinuation due to adverse events, this trend was not statistically significant (11.3% vs. 6.3%; P value not provided).

Dr. Axelrad

Don't ignore discontinuation rates

Jordan E. Axelrad, MD, assistant professor of medicine at NYU and a clinician at the Inflammatory Bowel Disease Center at NYU Langone Health, New York, commended the SEAVUE trial for its head-to-head design, which is a first for biologics in Crohn's disease.

"[T]his was a good undifferentiated group to understand what's the first biologic you should use in a patient with moderate to severe Crohn's disease. The primary, major take-home is that [ustekinumab and adalimumab] are similarly effective."

When asked about the slight superiority in minor secondary endpoints associated with ustekinumab, Dr. Axelrad suggested that rates of discontinuation deserve more attention.

"For me, maybe the major focus would be on the number of patients who stopped treatment," Dr. Axelrad said. "Although that was just numerical, that to me is actually more important." He also highlighted the lower injection burden associated with ustekinumab, which is given every 8 weeks, compared with every 2 weeks for adalimumab.

"A lot of the decision-making of where to position [ustekinumab in Crohn's disease] is going to come down to the payer," Dr. Axelrad said. "If there was a clear signal, providers such as myself would have a better leg to stand on, like we saw with VARSITY, where vedolizumab was clearly superior to adalimumab on multiple endpoints. We didn't see that sort of robust signal here."

The SEAVUE trial was supported by Janssen Scientific Affairs. Dr. Sands disclosed relationships with Janssen, AbbVie, Takeda, and others. Dr. Axelrad disclosed previous consulting fees from Janssen and research support from BioFire.

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CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

BY LUKE J. NAYAK, MD; ARJUN R. SONDHI, MD; AND MARIA WESTERHOFF, MD

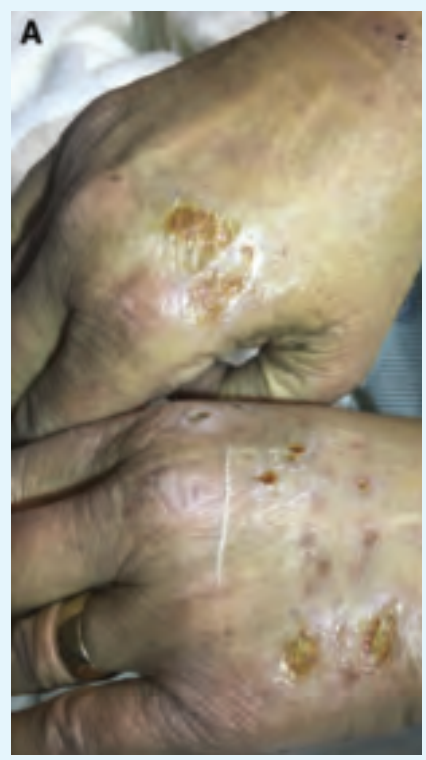
Previously published in Gastroenterology (2019 Sep1;157[3]:616-8).

A 66-year-old White woman with tetralogy of Fallot status after remote pulmonic valve surgery, hypothyroidism, and previous cholecystectomy presented to her primary care provider with 2 days of constant, dull, right upper–quadrant pain with nausea but without fever, association with meals, or association with defecation. Her home medications included low-dose aspirin and levothyroxine. Her physical examination revealed normal vital signs, a body mass index of 29 kg/m^2, right upper–quadrant tenderness to palpation without peritoneal signs, and normal bowel sounds. The remainder of her examination was normal.

The patient underwent an exhaustive evaluation beginning with laboratory tests, which revealed a normal complete blood count, basic metabolic panel, lipase, international normalized ratio, and urinalysis. Her liver function tests results showed aspartate aminotransferase 118 international IU/L, alanine aminotransferase 117 IU/L, alkaline phosphatase 147 IU/L, and total bilirubin 17.6 mg/dL, with a direct bilirubin of 11.9 mg/dL. Her liver function tests were last checked 18 months prior and were normal. A liver ultrasound examination revealed cirrhotic morphology without ascites or hepatic or portal vein thrombosis. A magnetic resonance imaging study of the liver revealed morphologic changes of hepatic cirrhosis without portal hypertension, biliary dilation, or stricturing. Additionally, hepatitis A IgM, hepatitis B surface antigen, hepatitis B core IgM and IgG, hepatitis C antibody, ceruloplasmin, antinuclear antibody, anti–smooth muscle antibody, anti–liver-kidney-microsomal antibody, quantitative immunoglobulins, antimitochondrial antibody, alpha-1 antitrypsin phenotype, phosphatidylethanolamine, serum protein electrophoresis, and alpha fetoprotein were reassuring. Later, the patient reported sensitivity to the sun, described as a "sun allergy" with irritation on her hands (Figure A). Mentation remained normal; however, given progressive worsening hepatic function evidenced by international normalized ratio of 1.7 and bilirubin of 27.6 mg/dL, the patient was urgently admitted for expedited portal manometry with transjugular liver biopsy. The hepatic venous pressure gradient was 23 mm Hg. The liver biopsy images are shown in Figure B, C.

What's the diagnosis?

The answer is on page 23.



AGA Clinical Practice Guidelines

Medical management of Crohn's

BY AMY KARON
MDedge News

For adult outpatients with moderate to severe Crohn's disease, new guidelines from the American Gastroenterological Association strongly recommend induction and maintenance therapy with anti–tumor necrosis factor–alpha agents or ustekinumab over no treatment.

"Although [related] evidence supporting infliximab and adalimumab was moderate certainty, the evidence for certolizumab pegol was low certainty," wrote Joseph D. Feuerstein, MD, of Beth Israel Deaconess Medical Center in Boston and his associates, on behalf of the AGA Clinical Guidelines Committee in Gastroenterology (2021 Jun;160[7]:2496-508). Vedolizumab received a conditional recommendation based on less robust evidence for induction in this setting.

Outcomes in Crohn's disease have improved, likely "because of earlier diagnosis, increasing use of biologics, escalation or alteration of therapy based on disease severity, and endoscopic management of colorectal cancer," Dr. Feuerstein and his associates wrote.

This update reflects these changes, strongly recommending biologic monotherapy over thiopurine monotherapy for induction. It also suggests "early induction with a biologic, with or without an immunomodulator, rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids." For the latter assessment, the guidelines noted that some studies were open label (which increases risk of bias) and that upfront combination therapy with a biologic and an immunomodulator could sometimes lead to overtreatment. Nonetheless, studies have shown associations between the step-up approach and "a potential risk of harm from disease progression related to inadequate disease therapy."

The guidelines also recommend that patients who have never received biologic drugs receive induction therapy with infliximab, adalimumab, or ustekinumab, rather than certolizumab pegol. This strong recommendation reflects the findings of a network meta-analysis conducted by the AGA in which certolizumab pegol was least effective, with no evidence for clear differences in efficacy among infliximab, adalimumab, and ustekinumab (Ann Int Med. 2013 Jul;159[2]:130-7). A network meta-analysis is a type of study that enables experts to compare therapies indirectly when head-to-head trials are lacking.

For patients who are naive to both biologics and immunomodulators, the guidelines suggest combination treatment with infliximab or adalimumab plus a thiopurine rather than monotherapy with either biologic. Because of a lack of randomized controlled trials, no recommendation is made regarding combination therapy with usteki-

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numab or vedolizumab.

For patients who have received but never responded to anti-TNF-alpha therapy (so-called primary nonresponders), ustekinumab is strongly recommended, and vedolizumab is conditionally recommended. For patients who initially responded to infliximab and then lost their response (secondary nonresponders), adalimumab and ustekinumab are strongly recommended, while vedolizumab receives another conditional recommendation.

For patients with moderate to severe luminal disease, induction and maintenance with infliximab, adalimumab, certolizumab pegol, vedolizumab, or ustekinumab are recommended over no treatment. Thiopurine monotherapy is suggested over no treatment for maintenance of remission, but not for induction. For methotrexate, subcutaneous or intramuscular monotherapy is suggested over no treatment. The sole available trial on oral methotrexate (12.5 mg/week) was negative, and "it is not clear if a higher dose would have been more effective," according to the guidelines. They strongly recommend against using 5-aminosalicytes or sulfasalazine because of lack of efficacy for maintaining remission and suggest not using natalizumab because of the risk of progressive multifocal leukoencephalopathy (PML). Corticosteroids are considered preferable to no treatment for induction but not for maintenance.

For patients with fistulizing disease, infliximab has "the most robust evidence" and receives a strong recommendation for induction and maintenance, while adalimumab, ustekinumab, and vedolizumab receive conditional recommendations. "In contrast, evidence suggests certolizumab pegol may not be effective for induction of fistula remission," the guidelines state. For patients with perianal disease with an active fistula but no abscess, combining biologics with antibiotics is strongly recommended over biologic monotherapy.

The guidelines define moderate to severe Crohn's disease as a Crohn's Disease Activity Index (CDAI) score of 220 or higher, the typical cutoff used in clinical trials. The recommendations apply to outpatient management, but in most cases would also apply to inpatients.

The recommendations apply to outpatient management, but in most cases would also apply to inpatients.

An expert commentary (Gastroenterology. 2021 Jun;160[7]:2557-62) accompanying the guidelines praises their "rigorous methods" based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Edith Y. Ho, MD, of Stanford (Calif.) University and her associates also laud the "innovative methods" that were used to compare treatments and assess data quality. In addition to the network meta-analysis, the guidelines set an a priori minimal clinically important difference (MCID) score of 10% for risk of treatment failure versus placebo. This led to more clinically relevant guidance, such as the conditional recommendation for vedolizumab in luminal disease since this drug did not meet the MCID threshold. Finally, the commentators emphasized that the guidelines are meant to facilitate, not dictate, treatment decisions: "Choice of therapies and treatment strategies will continue to rely on clinical judgment as well, and will continue to be informed by patient-specific values and preferences."

The AGA Institute was the sole source of funding. Four coauthors disclosed ties to Celgene, Takeda, Pendopharm, Merck Canada, Guardant Health, Ferring, and AbbVie. Dr. Feurstein and the other guidelines coauthors reported having no conflicts of interest. Some authors on the editorial disclosed relationships with AbbVie, Pfizer, and Janssen, but the remaining had no conflicts to disclose.

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CLINICAL CHALLENGES AND IMAGES

The diagnosis

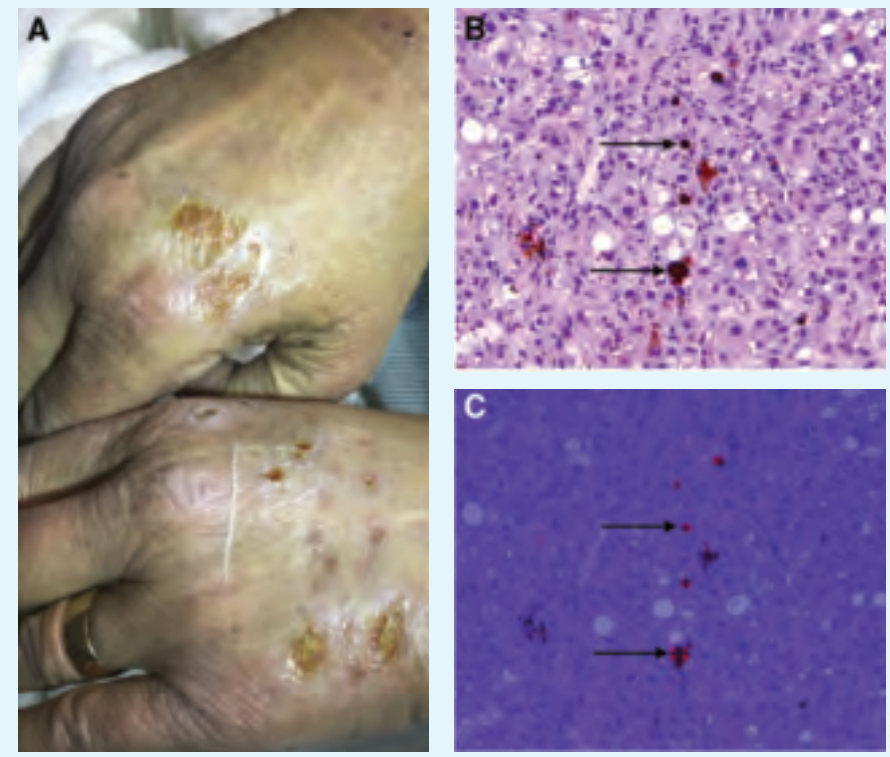
Answer to "What's your diagnosis?" from page 20: Erythropoietic protoporphyria.

Figure B demonstrated massive cholestasis with brown deposits that represented protoporphyrin precipitates, which plugged the bile ducts and led to a cholestatic pattern of liver injury. Under polarized light, protoporhyrin precipitates produced Maltese crosses (Figure C), which are pathognomonic of erythropoietic protoporphyria (EPP). Porphyria is a rare group of inherited heme biosynthesis disorders. EPP is an uncommon type of porphyria and is secondary to a ferrochelatase (FECH) gene mutation, which results in deficient activity of the mitochondrial enzyme FECH.[1]

FECH catalyzes chelation of iron into proptoporphyrin IX to form heme. The inability of protoporphyrins to be transformed into heme inhibits hepatic elimination and results in hepatocyte accumulation of protoporphyrins, leading to protoporphyrin precipitation in bile canaliculi. Painful photosensitivity (Figure A) is the most common manifestation of EPP, beginning in childhood.[2] Only a small proportion of patients with EPP develop liver dysfunction but the consequences can be severe.[2] Therefore, therapeutic decisions are based on limited published experience without randomized, controlled data.[2] One treatment method is to attempt to remove protoporphyrins from the blood via therapeutic plasma exchange.[2]

Our patient underwent one session of therapeutic plasma exchange; however, after this initial course of treatment, the patient's goals of care changed and she elected to enroll in hospice. Patients with severe liver dysfunction as a result of EPP require consideration of liver transplantation in the setting of fulminant hepatic failure. Liver transplantation does not cure EPP; the graft is at risk for similar EPP-related changes.[1] Only bone marrow transplantation can correct the underlying enzymatic defect in FECH.[1] Although physicians are often taught "common things are common," this case highlights a rare complication of a rare disease such as porphyria is an often forgotten or missed condition. Vigilance should be kept for other rare conditions, especially ones with curative treatments or fatal consequences. In an era where the role of liver biopsy is often questioned in favor of prediction models or noninvasive testing, we must have a low threshold to safely perform a liver biopsy when the diagnosis is unclear or a patient is deteriorating.

The quiz authors disclosed no conflicts of interest.



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