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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Northwestern University

Dr. Stephen B. Hanauer of Northwestern University and his colleagues provided updated guidance on use of thiopurines in IBD.

Clinical guidance: Thiopurine agents for the treatment of IBD

BY CALEB RANS

MDedge News

A new clinical practice update recommends combination therapy with tumor necrosis factor (TNF) inhibitors and thiopurines, as opposed to either therapy alone, for the treatment of ulcerative colitis (UC) and Crohn's disease (CD). The commentary was published in Gastroenterology.

Clinicians should also note that, while several clinical trials use weight-based dosing to monitor clinical response following thiopurine therapy, 6-thioguanine levels have been shown to better predict prognosis, wrote Stephen B. Hanauer, MD, AGAF of Northwestern University in Chicago and his colleagues.

The thiopurine drug class is composed of many different agents, including thioguanine, azathioprine, and mercaptopurine. Methotrexate, a folate antagonist affecting thymidylate production, is commonly used alongside thiopurines as steroid-sparing agents for patients with UC and CD. Among these therapies, various different dosing strategies and routes of administration are used to manage active disease.

Initially, thiopurines were studied exclusively as monotherapy for the treatment

See **Thiopurine** · *page 19*

PPI prophylaxis and placebo equal for GI bleeding

BY MADHU RAJARAMAN

MDedge News

There was no significant difference in mortality between critically ill patients who received pantoprazole prophylaxis for gastrointestinal bleeding, and those who received placebo, new findings suggest.

In a multicenter, randomized trial of 3,298 adult patients at risk for gastrointestinal bleeding, 510 patients (31.1%) in the pantoprazole group and 499 (30.4%) in the placebo group had died at 90 days (relative risk, 1.02; 95% confidence interval, 0.91-1.13; $P = .76$). The results were published in the New England Journal of Medicine.

Patients were aged 18 years or older; had been admitted to the ICU for an acute condition in one of six international centers; and had at least one risk factor for gastrointestinal bleeding including shock, use of anticoagulant agents, renal replacement therapy, mechanical ventilation (expected to last more than 24 hours), any history of liver disease, or any history of or ongoing coagulopathy. A total of 1,645 patients were randomly assigned to receive 40 mg of intravenous pantoprazole once daily and 1,653 received placebo, reported Mette Krag, MD, of the department of intensive care at Rigshospitalet in Copenhagen, and her coauthors.

The primary outcome

See **PPI** · *page 22*

INSIDE

Two probiotic products don't prevent gastroenteritis in children, studies show

BY ANDREW D. BOWSER

MDedge News

Two probiotic products containing strains of *Lactobacillus rhamnosus* failed to prevent moderate to severe gastroenteritis in children, according to the results of large, randomized trials published in the New England Journal of Medicine.

Neither probiotic formulation significantly reduced duration of diarrhea or vomiting, or improved endpoints such as day-care absenteeism in the double-blind, placebo-controlled trials, which together included 1,857 infants or children with acute infectious gas-

See **Probiotic** · *page 20*

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LETTER FROM THE EDITOR: Packed with science


DR. ALLEN

This month's issue is packed with important science – nice to get back to medicine and not focus on politics. On page one, we highlight new clinical guidance on the use of thiopurines in inflammatory bowel disease. This clinical practice update has some very specific and clear recommendations about thiopurines, especially in combination with biologic agents. As any clinician knows, treatment of IBD has become complex from both a biologic standpoint and because we now recognize the importance of social determinants of health in our management of chronic diseases. We have seen an enormous outpouring of work that helps gastroenterologists develop multidisciplinary "homes" for IBD patients. These programs are now becoming best practice standards. Such approaches are practical for both academic and community GI practices. Best practice for our IBD patients now involves following clinical guidelines, understanding the impact of IBD on patients' social and behavioral health and the incorporation of support services (or referral), and outcomes measurement. This clinical practice update will help us enhance our medical therapy for patients with both Crohn's disease and ulcerative colitis.

Other stories include a review of the new AGA clinical practice update on endoscopic submucosal dissection for early-stage cancers with important information about technique, indications, and management of complications. Questions about our approach to prevention of GI bleeding for patients in the ICU by a new multicentered trial of PPI use in over 3,500 patients. Essentially, PPI prophylaxis should be reserved for seriously ill patients at high risk for bleeding – prophylaxis may not be needed in other ICU patients. Finally, another study does not support use of probiotics (at least in the current formulation) in children with gastroenteritis.

I hope you enjoy the issue and that you had a wonderful year's end. We look forward to more excitement in 2019.

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

DDSEP eight

Quick quiz

Q1. A 31-year-old man is seen for a 1-week history of epigastric pain and scleral icterus. One month earlier, he developed diarrhea and fatigue, which has continued to persist. He denies any prior medical problems, though he admits he has not seen a doctor in years. He is currently visiting family in the United States, but he resides in South Africa. His laboratory tests are as follows: total bilirubin, 3.5 mg/dL; direct bilirubin, 2.9 mg/dL; alkaline phosphatase, 720 U/L; ALT, 105 U/L; AST, 117 U/L; albumin, 2.1 g/dL; INR, 1.2; HIV viral load, 450,000 copies/mL; CD4 count, 25 cells/mm^3. An abdominal ultrasound shows intra- and extrahepatic ductal dilation and an ERCP shows strictured intrahepatic ducts with papillary stenosis.

Which of the following organisms is most likely to be associated with this condition?
A. Microsporidia
B. Ascaris
C. Cryptosporidium
D. Cyclospora
E. Mycobacterium

Q2. A 54-year-old woman presents for management of moderately severe ileocolonic Crohn's disease. She has a strong family history of multiple sclerosis and recently noted some tingling in her toes for which she is undergoing neurologic evaluation. She has had two small basal cell carcinomas removed from her cheek in the last year. She received the BCG vaccine as a child and had a positive PPD skin test within the last year. Laboratory evaluation reveals HBsAg negative, anti-HBs positive, and anti-HBc positive; JC virus antibody is positive.

Which of the following is the strongest reason to avoid anti-TNF therapy in this patient?
A. Current neurologic symptoms
B. History of skin cancer
C. Positive PPD skin test
D. Infection with hepatitis B
E. Presence of JC virus antibody

The answers are on page 29.

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FROM THE AGA JOURNALS

Routine markers predicted response to OCA in NASH

BY AMY KARON
MDedge News

Routine clinical and laboratory markers predicted histologic response to obeticholic acid (OCA) therapy among patients with nonalcoholic steatohepatitis (NASH), investigators reported in the January issue of Gastroenterology.

In a secondary analysis of data from the FLINT trial, histologic response at treatment week 24 correlated significantly with baseline nonalcoholic fatty liver disease activity score (NAS) greater than 5, baseline triglycerides 154 mg/dL or less, baseline international normalized ratio no greater than 1, baseline aspartate aminotransferase level no greater than 49 U/L, and at least a 17-U/L decrease from baseline in alanine aminotransferase level.

A stepwise logistic regression model including these variables and receipt of OCA distinguished histologic responders from nonresponders with an area under the receiver operating characteristic curve of 0.83 (95% confidence interval, 0.77-0.89; *P* less than .0001). These parameters "are readily available clinical and biochemical characteristics that are routinely available to clinicians and may be applied to daily practice," wrote Rohit Loomba, MD, of the University of California, San Diego, with his associates. They may show "that the patients most likely to achieve histologic response are those with higher disease activity, but still with largely conserved liver function, allowing for potential healing or improvement."

NASH is expected to become the leading reason for liver transplantation in the next few decades. Several treatments can induce histologic hepatic improvement, but none are approved for NASH. OCA (Ocaliva) is a selective agonist of the farsenoid X receptor ligand and is indicated for primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA).

In the 72-week, multicenter, randomized, double-blind FLINT trial, noncirrhotic adults with biopsy-confirmed NASH received once-daily OCA (25 mg) or placebo. Blinded pathologists interpreted biopsies. The primary endpoint (improvement in liver histology) was met in the interim analysis, so the researchers stopped collecting final liver biopsies.

The secondary analysis included all patients with baseline and final biopsies, including 73 histologic responders and 127 nonresponders. "[The] trends for each of the selected predictors was the same when comparing histologic responders to nonresponders, regardless of treatment group (OCA versus placebo)," the researchers wrote. The predictors are biologically feasible, the researchers contended – for example, high baseline NAS would be more susceptible to significant improvement, while lower baseline triglyceride levels might reflect a liver that "is less burdened by triglyceride secretion" and, therefore, might have greater capacity to heal. Both AST and ALT "are metrics of liver injury," and lower baseline AST, in combination with greater reduction in ALT at week 24, probably reflected "AST and ALT levels that are closer to normal," they added.

The researchers acknowledged several possible sources of bias. Trial participants were recruited from tertiary care settings and had complete biopsy data, which might not reflect the overall NASH population. Overfitting also could have biased the model because the number of variables assessed approached the number of events being predicted. Furthermore, the model assessed no treatment other than OCA. "A more robust model could potentially be developed if multiple pharmacological interventions could be considered simultaneously," the researchers noted. The ongoing phase 3 REGENERATE trial aims to confirm the benefit of OCA in patients with NASH, they added. Topline results are expected in October 2022.

The FLINT trial was funded by Intercept Pharmaceuticals and the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Loomba cochaired the FLINT trial protocol-writing committee, is on the steering committee of the ongoing REGENERATE trial, and has received research funding from Intercept Pharmaceuticals, which developed and markets OCA. Several other coinvestigators reported ties to Intercept and to other pharmaceutical companies.

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SOURCE: Loomba R et al. Gastroenterology. 2018 Sep 14. doi: 10.1053/j.gastro.2018.09.021.

Use ESD for early-stage esophageal cancer

BY AMY KARON
MDedge News

For patients with early-stage esophageal squamous cell carcinoma, minimally invasive esophageal submucosal dissection (ESD) led to significantly fewer severe adverse perioperative events than esophagectomy and was associated with similar rates of all-cause mortality and cancer recurrence or metastasis, according to the findings of a single-center retrospective cohort study.

After a median of 21 months of follow-up (range, 6-73 months), rates of all-cause mortality were 7% with ESD and 11% with esophagectomy, said Yiqun Zhang of Zhongshan Hospital, Shanghai, China, and his associates. Rates of cancer recurrence or metastasis were 9.1% and 8.9%, respectively, while disease-specific mortality was lower with ESD (3.4% vs. 7.4% with esophagectomy; *P* = .049). Severe nonfatal adverse perioperative events occurred in 15% of ESD cases versus 28% of esophagectomy cases (*P* less than .001). The findings justify more studies of ESD in carefully selected patients with early-stage (T1a-m2/m3 or T1b) esophageal squamous cell carcinoma, the researchers wrote in the January issue of Clinical Gastroenterology and Hepatology.

Esophagectomy is standard for managing

Continued on following page

This study adds more evidence supporting the use of endoscopic submucosal dissection (ESD) in early esophageal cancer. Unlike esophageal adenocarcinoma, esophageal squamous cell carcinoma (ESCC) has a higher risk of lymph node metastasis and tends to be multifocal. ESCC lesions invading the submucosa (T1b) have the highest risk of lymph node metastasis (up to 60% in lesions with deep submucosal invasion).

DR. OTHMAN

Historically, endoscopic resection was reserved for mucosal tumors while submucosal tumors were managed surgically. Several trials have investigated the role of ESD in ESCC limited to the mucosa with excellent results. However, data for ESCC invading the submucosa (T1b lesions) are lacking. This study included 596 patients, almost half of included patients (282 patients) had T1b lesions. Although most of the T1b lesions were treated surgically (200 patients), there was a large cohort of 82 T1b ESCC lesions treated by ESD.

Interestingly, there was no difference in tumor recurrence or overall mortality in patients treated with ESD, compared with surgery for both mucosal and submucosal lesions.

Another interesting finding in this study was the use of adjuvant treatment such as radiotherapy and chemotherapy for patients treated with ESD who were found to have evidence of lymphovascular invasion. The outcome of this subset of patients was not different from patients who underwent esophagectomy. Recent evidence from this study and other published data suggest that there is a subset of submucosal ESCC lesions that can be managed endoscopically, especially submucosal lesions limited to the upper third of the submucosa. Further studies investigating the role of adjuvant treatment after ESD for deep submucosal lesions or lesions with lymphovascular invasion are needed.

Mohamed O. Othman, MD, is an associate professor of medicine, director of advanced endoscopy, and chief of the section of gastroenterology, Baylor College of Medicine, Houston. He is a consultant for Olympus and Boston Scientific.

FROM THE AGA JOURNALS

On-time screening may cut risk of death from CRC

BY AMY KARON
MDedge News

Patients who died from colorectal cancer (CRC) were significantly more likely than controls not to have been screened, to have missed screenings, or not to have followed up on an abnormal result, according to the results of a large retrospective case-control study.

The findings signify "potentially modifiable" screening failures in a population known for relatively high uptake of CRC screening, wrote Chyke A. Doubeni, MD, MPH, of the University of Pennsylvania, Philadelphia, and his associates in the January issue of Gastroenterology. Strikingly, 76% of patients who died from CRC were not current on screening versus 55% of cancer-free patients, they said. Being up to date on screening decreased the odds of dying from CRC by 62% (odds ratio, 0.38; 95% confidence interval, 0.33-0.44), even after adjustment for race, ethnicity, socioeconomic status, comorbidities, and frequency of contact with primary care providers, they added.

Colonoscopy, sigmoidoscopy, and fecal testing are effective and recommended screening techniques that help prevent deaths from CRC. Therefore, most such deaths are thought to result from "breakdowns in the screening process," the researchers wrote. No prior study has examined detailed screening histories and their association with CRC mortality.

Accordingly, the researchers reviewed medical records and registry data for 1,750 enrollees in the Kaiser Permanente Northern and Southern California systems who died from CRC during 2006-2012 and were part of the health plan for at least 5 years before their cancer diagnosis. They compared these patients with 3,486 cancer-free controls matched by age, sex, study site, and numbers of years enrolled in the health plan. Patients were considered up to date on screening if they were screened at intervals recommended by the 2008 multisociety CRC screening guidelines – that is, if they had received a colonoscopy within 10 years of CRC diagnosis or sigmoidoscopy or barium enema within 5 years of it. For fecal testing, the investigators used a 2-year interval based on its efficacy in clinical trials.

Among patients who died from CRC, only 24% were up to date on screening versus 45% of cancer-free patients, the investigators determined. Furthermore, 68% of patients who died from CRC were never screened or were not screened at appropriate intervals, compared with 53% of cancer-free patients.

Although 8% of CRC deaths occurred in patients who had not followed up on abnormal screening results, only 2% of controls had not followed up on abnormal screening results.

"This study suggests that, even in settings with high screening uptake, access to and timely uptake of screening, regular rescreening, appropriate use of testing given patient characteristics, completion of timely diagnostic testing when screening is positive, and improving the effectiveness of screening tests, particularly for right colon cancer, remain important areas of focus for further decreasing [colorectal cancer] deaths."

The National Institutes of Health funded the work. The investigators reported having no conflicts of interest except that one coinvestigator is co-editor in chief of the journal Gastroenterology.

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SOURCE: Doubeni CA et al. Gastroenterology. 2018 Sep 27. doi: 10.1053/j.gastro.2018.09.040.

Screening for colorectal cancer (CRC) is a major success story – one of only two cancers (the other being cervical cancer) with an A recommendation for screening from the U.S. Preventive Services Task Force. Multiple randomized trials for two CRC screening modalities, stool-based tests and sigmoidoscopy, have shown significant reductions in CRC incidence and mortality. Additionally, U.S. CRC incidence and mortality rates have been steadily decreasing for the past several decades, with much of that decrease attributed to screening.


DR. PINSKY

Within this context, Doubeni et al. examined the association of CRC screening with death from CRC in a real-world HMO setting. Their study is notable for several reasons. First, it showed a highly protective effect on CRC mortality of being up to date with screening (odds ratio, 0.38; 95% confidence interval, 0.33-0.44). Second, it examined CRC screening as a process, with various steps of that process related to CRC mortality. Finally, methodologically, the study's utilization of electronic medical records and cancer registry linkages highlights the importance of integrated data systems in the efficient performance of epidemiologic research.

Of note, screening was primarily stool-based tests (fecal occult blood test/fecal immunochemical test) and sigmoidoscopy, in contrast to most of the U.S., where colonoscopy is predominant. Randomized trials of these modalities show mortality reductions of 15%-20% (FOBT/FIT) and 25%-30% (sigmoidoscopy), respectively. Therefore, some of the reported effect is likely due to selection bias, with healthier persons more likely to choose screening.

It would be of interest to see similar studies performed in a colonoscopy-predominant screening setting and with the effect on CRC incidence as well as mortality examined.

Paul F. Pinsky, PhD, chief of the Early Detection Research Branch, National Cancer Institute, Bethesda, MD. He has no conflicts of interest.

Continued from previous page

early-stage esophageal squamous cell carcinoma but is associated with high morbidity and mortality. While ESD is minimally invasive, it is considered risky because esophageal squamous cell carcinoma so frequently metastasizes to the lymph nodes, the investigators noted. For the study, they retrospectively compared 322 ESDs and 274 esophagectomies performed during 2011-2016 in patients with T1a-m2/m3 or T1b esophageal squamous cell carcinoma. All cases were pathologically confirmed, and none were premalignant (that is, high-grade intraepithelial neoplasias).

ESD was associated with significantly lower rates of esophageal fistula (0.3% with ESD vs. 16% with esophagectomy; *P* less than .001) and pulmonary complications (0.3% vs. 3.6%, respectively; *P* less than .001), which explained its overall superiority in terms of severe adverse perioperative events, the researchers wrote. Perioperative deaths were rare but occurred more often with esophagectomy (four patients) than with ESD (one patient). Depth of tumor invasion was the only significant correlate of all-cause mortality (hazard ratio for T1a–m3 or deeper tumors versus T1a–m2 tumors, 3.54; 95% CI, 1.08-11.62; *P* = .04) in a Cox regression analysis that accounted for many potential confounders, such as demographic and tumor characteristics, hypertension, chronic obstructive pulmonary disease, nodal metastasis, chemotherapy, and radiotherapy.

Perhaps esophagectomy did not improve survival in this retrospective study because follow-up time was too short, because adjuvant therapy compensated for the increased risk of tumor relapse with ESD, or because of the confounding effects of unmeasured variables, such as submucosal stages of T1b cancer, lymphovascular invasion, or tumor morphology, the researchers wrote. "Since a randomized study comparing esophagectomy and ESD alone would not be practical, a potential strategy for future research may include serial treatments – that is, ESD first, followed by esophagectomy, radiotherapy, or chemotherapy, depending on the ESD pathology findings," they added. "A quality-of-life analysis of ESD would also be helpful because this might be one of the biggest advantages of ESD over esophagectomy."

The study was supported by the National Natural Science Foundation of China, the Shanghai Committee of Science and Technology, and Zhongshan Hospital. The investigators reported no conflicts of interest.

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SOURCE: Zhang Y et al. Clin Gastroenterol Hepatol. 2018 Apr 25. doi: 10.1016/j.cgh.2018.04.038.

FROM THE AGA JOURNALS

Vedolizumab, tofacitinib induced rapid improvements in IBD symptoms

BY AMY KARON
MDedge News

Two recent studies highlight the ability of vedolizumab and tofacitinib to rapidly improve symptoms reported by patients with inflammatory bowel disease (IBD).

In a post hoc study of 1,758 patients with ulcerative colitis (UC) or Crohn's disease (CD) in the phase 3 GEMINI trials, 2 weeks of vedolizumab (Entyvio) therapy effectively improved patient-reported outcomes, and these continued to improve through 6 weeks of treatment, wrote Brian G. Feagan, MD, and his associates in the January issue of Clinical Gastroenterology and Hepatology.

In UC patients who had not previously received tumor necrosis factor (TNF) antagonists, 22% of vedolizumab recipients, compared with 7% of placebo recipients, achieved complete resolution of rectal bleeding together with a meaningful reduction in stool frequency at treatment week 2, the investigators noted. Among CD patients who were naive to TNF antagonists, 15% reported decreases in abdominal pain and loose stools at treatment week 2, compared with 8% of placebo recipients.

Although 2 weeks of vedolizumab also topped placebo for improving patient-reported outcomes among TNF antagonist–exposed patients, the effects were less pronounced, wrote Dr. Feagan, of the University of Western Ontario, London, and his associates. "These data add to the growing evidence that second-generation biologics, such as vedolizumab and ustekinumab, have higher efficacy in TNF antagonist–naive patients in both clinical trials and real-world settings. Recent trends in clinical practice are moving toward incorporating disease-modifying therapy earlier in the treatment of IBD to prevent disease progression and cumulative bowel damage."

Patient-reported outcomes have become key during both clinical research and regulatory review of claims on proposed drug labels. In the second study, also published in the January issue of Clinical Gastroenterology and Hepatology, Stephen B. Hanauer, MD, of Northwestern University, Chicago, and his associates performed a post hoc analysis of symptoms reported by 1,139 adults with UC who received the oral small-molecule Janus kinase inhibitor tofacitinib (10 g twice daily) or placebo during the 8-week OCTAVE Induction 1 and 2 trials. These were identical phase 3 studies of patients with moderate to severe UC who could not tolerate or had responded inadequately to TNF antagonists, corticosteroids, or thiopurines.

Compared with placebo, 3 days of tofacitinib therapy induced significantly greater reductions from baseline in patient-reported stool frequency and rectal bleeding (*P* less than .01 for each measure), Dr. Hanauer and his associates reported. The effect was independent of prior treatment for UC or baseline levels of C-reactive protein. These findings reflect the rapid onset of effect of tofacitinib therapy in patients with UC. In contrast, thiopurines (azathioprine and 6-mercaptopurine) can take at least 8 weeks to exhibit steroid-sparing effects.

While corticosteroids can induce UC remission within 5 days, their side effects tend to escalate over time and they "lack maintenance benefits," the researchers wrote. "In these analyses, onset of tofacitinib efficacy occurred within 3 days, irrespective of concomitant corticosteroid use or prior anti-TNF treatment failure."

Takeda funded the GEMINI studies. Dr. Feagan reported advisory relationships with Takeda, AbbVie, Amgen, AstraZeneca, and several other pharmaceutical companies. Dr. Hanauer also reported ties to numerous pharmaceutical companies, including Pfizer, which funded the OCTAVE trials.

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SOURCES: Feagan BG et al. Clin Gastroenterol Hepatol. 2018 May 29. doi: 10.1016/j.cgh.2018.05.026; Hanauer SB et al. Clin Gastroenterol Hepatol. 2018 Jul 15. doi: 10.1016/j.cgh.2018.07.009.

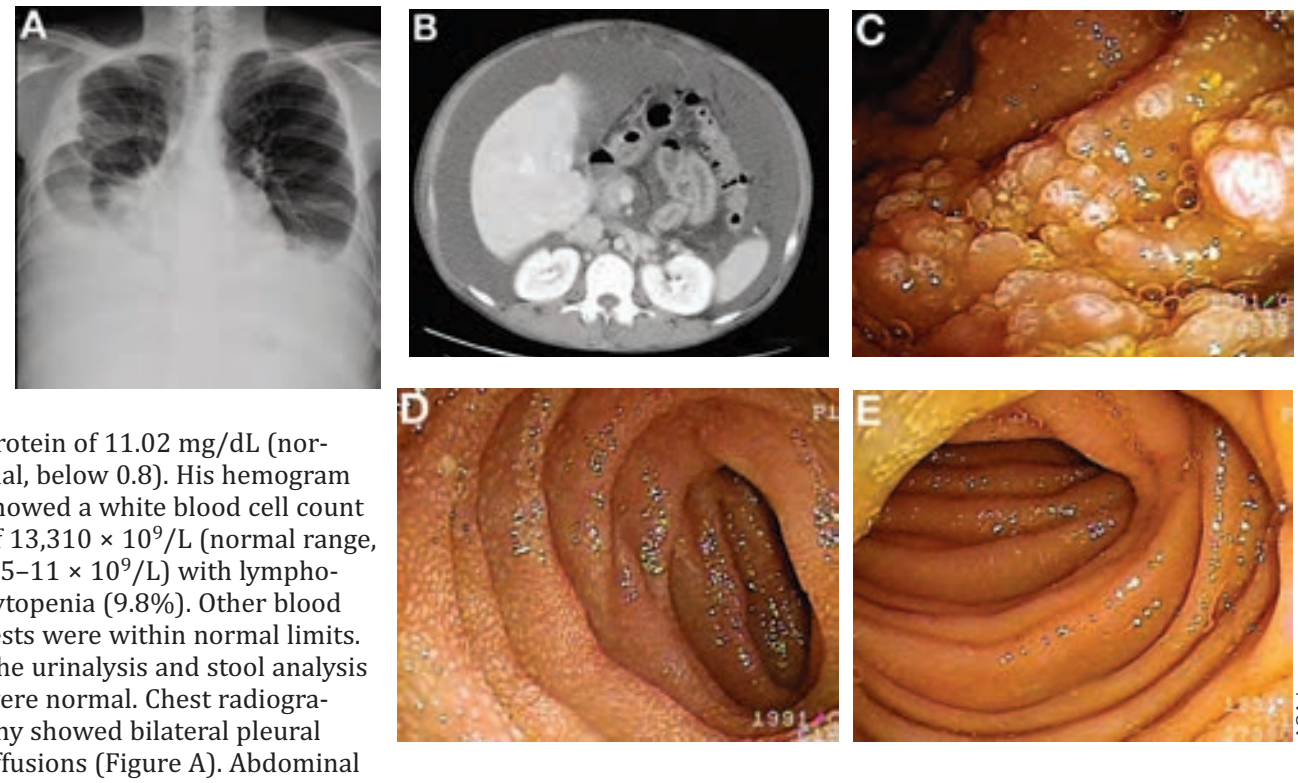
CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

By Jen-Wei Chou, MD, Ken-Sheng Cheng, MD, and Ching-Pin Lin, MD. Published previously in Gastroenterology (2017;152[1]:31-3).

A 19-year-old boy presented to our hospital because of a 6-month history of progressive dyspnea and generalized edema. He developed cough, abdominal fullness, diarrhea, and leg edema 5 years ago. Liver cirrhosis was suspected at that time. However, he seemed to have a poor response to medical treatment. Physical examination showed decreased breathing sounds and rales of the bilateral lower chest area, a distended abdomen with multiple purple striae, and edema of bilateral lower legs.

Laboratory tests showed a low serum total protein of 3.8 g/dL (normal range, 5.5–8), albumin of 2.0 g/dL (normal range, 3.8–5.4), total calcium of 7 mg/dL (normal range, 8.4–10.8), C-reactive protein of 11.02 mg/dL (normal, below 0.8). His hemogram showed a white blood cell count of 13,310 × 10^9/L (normal range, 3.5–11 × 10^9/L) with lymphocytopenia (9.8%). Other blood tests were within normal limits. The urinalysis and stool analysis were normal. Chest radiography showed bilateral pleural effusions (Figure A). Abdominal computed tomography demonstrated large ascites (Figure B). Paracentesis showed his serum ascites albumin gradient was 1.9 g/dL. Subsequently, antegrade double-balloon enteroscopy (Fujinon EN-450T5; Fujinon, Saitama, Japan) demonstrated nodular mucosal lesions with a milk-like surface in the duodenum (Figure C). Moreover, a snowflake appearance of mucosa was found in the jejunum and proximal ileum (Figure D). However, normal appearance of mucosa was identified in the middle ileum (Figure E). Biopsy specimens from these abnormal mucosal lesions were taken for pathology.



See the diagnosis on page 28.

AGA to FDA: We support new labeling recommendations for probiotics

In a new comment letter to FDA, AGA commends FDA's recent draft guidance – "Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials" – clarifying the expectations of probiotics manufacturers who choose to specify the amount of a live microbial component in their product in colony-forming units (CFUs).

Though manufacturers are not currently required to report CFUs, AGA feels strongly that all manufacturers of probiotic supplements should voluntarily report the composition of live microbials in their products as CFUs.

However, reporting CFUs alone provides insufficient information to consumers and health care professionals who may recommend probiotic supplements to their patients. In our comment letter, AGA encourages FDA to expand what information manufacturers are required to include. In addition to the conditions already outlined in FDA's draft guidance, AGA recommends including the conditions of storage as well as an expiration or "use by" date.

We acknowledge that researchers are evaluating other methods and units of measure besides CFUs for not only live microbials but also microbial bioactivity. However, in the absence of a widely accepted alternative, which may take several years to develop and adopt, AGA strongly encourages FDA and manufacturers to take the small step forward of using CFUs now rather than waiting for another solution to emerge.

Probiotics have been an important focus for the AGA Center for Gut Microbiome Research and Education due to the need for evidence-based guidance for health care providers and their patients. The center will continue to work to educate physicians, patients and industry on best practices to ensure safe use of probiotics.

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Rising microbiome investigator: Lea Ann Chen, MD

We spoke with Dr. Chen, assistant professor of medicine at New York University and the recipient of the AGA Research Foundation's 2016 Research Scholar Award, to learn about her work on the gut microbiome and inflammatory bowel disease (IBD).

How would you sum up your research in one sentence?
I study longitudinal changes of the gut microbiome as it relates to gastrointestinal illnesses, particularly IBD.

What impact do you hope your research will have on patients?
I hope that my research will provide greater insights into the role of gut microbes in disease pathogenesis and activity to ultimately inform the development of new diagnostics and treatments.

What inspired you to focus your research career on the gut microbiome?
I've long been fascinated by ecological systems and host-microbe interactions. As technologies to study the gut microbiome became more readily available, I was eager, and somewhat relieved, to be able to combine my research interests with my clinical interest in gastroenterology.

What recent publication from your lab best represents your work, if anyone wants to learn more?
In this study, we show that gut bacterial disturbances are resolved after fecal transplantation in children without IBD but are only transiently resolved in those with IBD.

Hourigan S., Chen L.A., Grigoryan Z., et al. Microbiome changes associated with sustained eradication of *Clostridium difficile* after fecal microbiota transplantation in children with and without inflammatory bowel disease. Aliment Pharmacol Ther. 2015;42:741-52.

You're involved with several AGA initiatives including the Future Leaders Program and the FMT National Registry. How has being an AGA member impacted your career?
AGA has provided key mentorship and training opportunities that have been instrumental in my career development. It has further helped me discover a diverse community of clinicians and scientists who are amazing role models, resources and colleagues. I really had no inkling what was in store when I first joined AGA as a trainee, but I feel very lucky that I did and am grateful for how AGA membership has really enriched my life as a gastroenterologist.

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Memorial and honorary gifts: A special tribute

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

- **Giving a gift to the AGA Research Foundation in memory of a loved one.** A memorial gift is a meaningful way to celebrate the legacy of a family member, friend, or colleague.
- **A gift today.** An outright gift will help fund the AGA Research Awards Program. Your gift will assist in furthering basic digestive disease research which can ultimately advance research into all digestive diseases. The financial benefits include an income tax deduction and possible elimination of capital gains tax.

Learn more about ways to recognize and acknowledge someone by visiting our website at www.gastro.org/contribute or contact Harmony Excellent at 301-272-1602 or hexcellent@gastro.org.

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New editors appointed to *CMGH*

Congratulations to Klaus H. Kaestner, PhD, MSc, and Michael A. Pack, MD, new co-editors-in-chief of *Cellular and Molecular Gastroenterology and Hepatology* (*CMGH*).

The next editorial team of the AGA's basic and translational journal *CMGH* has been selected. Both editors are from the University of Pennsylvania Perelman School of Medicine. Dr. Kaestner is the Thomas and Evelyn Suor Butterworth Professor in Genetics. Dr. Pack is a professor of medicine and cell and developmental biology and is an attending gastroenterologist at the Hospital of the University of Pennsylvania.

CMGH debuted in 2015 with the mission of publishing impactful digestive biology research that ranges from mechanisms of normal function to pathobiology and covers a broad spectrum of themes in gastroenterology, hepatology, and pancreatology. *CMGH* is open access, published eight times a year, online-only and is indexed in Medline and PubMed Central. Carrying forward the tremendous success of the journal's current editor-in-chief, Jerrold R. Turner, MD, PhD, AGAF, and his board of editors, Dr. Kaestner and Dr. Pack's goals include advancing the impact and reputation of *CMGH*, ensuring the quality and fairness of the peer-review process and introducing new content that is important to the basic and translational research community.

Dr. Kaestner

Dr. Pack

Dr. Kaestner and Dr. Pack's board of editors includes:

Jonathan Katz, MD
Perelman School of Medicine, University of Pennsylvania

Alison Simmons, MD, PhD
University of Oxford

Frank Tacke, MD, PhD
Rheinisch-Westfälische Technische University

In response to the appointment, Dr. Kaestner said, "We are extremely excited about the opportunity to build on the success of the current editorial team, which has already made *CMGH* a go-to journal for outstanding digestive disease research. Our goals will be to extend the reach of the journal and to ensure its growth as the premier publication for basic research in gastroenterology and hepatology."

Dr. Pack added, "The remarkable success achieved by CMGH is a testament to the skill and dedication of Dr. Turner and his associate editors, Drs. Goldenring, Rescigno and Wells, as well as the tremendous growth of impactful basic research in digestive organ biology and disease. Dr. Kaestner and I look forward to maintaining the retiring editorial team's standard of excellence as we expand the *CMGH* readership and its visibility in the basic research community."

Dr. Kaestner and Dr. Pack will begin their term in July 2019.

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Top AGA Community patient cases

Physicians with difficult patient scenarios regularly bring their questions to the AGA Community (https://community.gastro.org/discussions) 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. Active colitis in a patient with previous colon cancer (http://ow.ly/M2IW30mRonV)
This popular conversation centers around next steps for a 39-year-old previously treated for a large malignant tumor with a right hemicolectomy and chemotherapy. She was referred for a chromoendoscopy, which revealed four areas of nonpolypoid abnormal mucosa with indistinct borders and abnormal dye uptake. Biopsies also revealed low-grade dysplasia and minimally active colitis.

2. IBD in remission (http://ow.ly/9XXy30mRow7)
A 66-year-old female with a history of Crohn's disease is currently asymptomatic and in remission, but with low Remicade trough. The debate among physicians in the forum questions the need for further action or follow-up insight.

3. Eosinophilic esophagitis and duodenitis (http://ow.ly/kja130mRoDV)
This 40-year-old patient was originally seen for food bolus. The physician prescribed proton pump inhibitors (PPI) after a scope showed typical eosinophilic esophagitis (EoE) findings. Although he had symptoms of obstruction since he was 15, this was his first upper endoscopy. Biopsies following successful scopes showed eosinophilic duodenitis and the patient had no signs of eosinophilia in the stomach.

4. Eosinophilic esophagitis and gastric sleeve (http://ow.ly/Tna230mRoQv)
A physician noted no established absolute contraindication for a 50-year-old patient who was seen for a presleeve gastrectomy. Others contributing to this thread shared concerns for the risk for gastroesophageal reflux disease (GERD) post surgery and committing the patient to long-term steroids.

More clinical cases and discussions are at https://community.gastro.org/discussions.

A clinician's guide to microbiome testing

BY ALEXANDER KHORUTS, MD

The intestinal microbiota, also commonly known as the "gut microbiome" is integral to human physiology and has wide-ranging effects on the development and function of the immune system, energy metabolism and nervous system activity. There is a lot of excitement around the potential of targeting the microbiome therapeutically to promote health and to prevent or treat medical conditions. Further, as DNA sequencing technologies and computational methods continue to improve (as reviewed by Rob Knight and colleagues in a prior editorial), there is significant interest in developing microbiome-based diagnostics for clinical applications.

The industry has recognized the consumer interest in microbiome-based diagnostics as an opportunity, and a number of commercial laboratories are marketing tests directly to patients. Physicians, particularly gastroenterologists, are increasingly being asked by their patients to help interpret such test reports; in some cases, the patient may even request a physician order to purchase the tests for insurance coverage or other reasons.

Earlier this year, AGA members had a robust discussion in the AGA Community about microbiome-based tests, requirements for physician authorization, and the clinical utility (if any) of the results of such tests. The discussion inspired the development of a primer for clinicians on microbiome testing, which my colleagues and I recently published. Key takeaways from our publication are summarized below.

Limitations of microbiome sequencing. Microbiome datasets have the same limitations as any other sample-dependent dataset. First and foremost, a single stool sample will tell you something about a person's microbiome profile only at the time and location that the sample was collected. How the sample was collected and how it was stored may significantly impact the analysis. The analysis generally provides an overview of bacterial families and genera, but little information about the viruses, protozoa and fungi. Furthermore, stool analysis may not reflect well the microbiome composition at the mucosal surface in the intestine. As a result, a single analysis of an individual stool sample merely provides a snapshot of the fecal microbiome that is incomplete and extremely limited in what we can learn from it.

"Good" vs. "bad." The reports resulting from microbiome-based tests often describe the patient's microbiome profile in terms of how much "good" and "bad" bacteria are present. This kind of a classification framework represents a naive and cartoonish view of the microbial world. Instead, it is important to appreciate microbial communities as functional networks, and that their functionality cannot be defined as a mere summation of individual microorganisms. Microbes, just like people, vary their behavior in accordance with the context that may be provided by the activity of other microbes and the host. Whether a particular species or strain is helpful or harmful depends on what other bacteria are present, their density, how they interact with each other (e.g., are they mutually beneficial or competitive?) and factors from the human host such as their diet or immune system activity. For example, *Clostridioides difficile* is a potential pathogen, yet it also naturally exists in the intestines of many people as a nonharmful, commensal species. Its pathogenic potential depends on the state of the other intestinal microbes and host factors, such as presence of anti-*C. difficile* toxin antibodies.

A single stool sample will tell you something about a person's microbiome profile only at the time and location that the sample was collected. How the sample was collected and how it was stored may significantly impact the analysis. The analysis generally provides an overview of bacterial families and genera, but little information about the viruses, protozoa and fungi.

Importantly, microbiome tests, which generally provide only a low-resolution microbial community overview, are not designed for pathogen identification. That is best done with targeted diagnostics. Even then, as well illustrated by the *C. difficile* example, diagnosis of an infection cannot be made on the basis of laboratory testing alone and requires clinical information.

Taxonomy vs. function. Current technology allows a fairly inexpensive characterization of most bacterial taxa (at family and genus levels). However, taxonomy is not easily translated into functional information. Different taxa of microbes may be able to execute the same chemical transformations. In contrast, functional information depends on the genes present and how much are these genes expressed. However, obtaining this kind of information is much more resource intensive. Measurements of metabolites may also provide very valuable functional information, but proper sample collection for metabolomics is much more difficult.

Interindividual variability. The consistent lesson we've learned from the microbiome literature is that there is not a single "healthy" microbiome profile. We have not identified a particular microbiome profile that is predictive of a particular disease, though many researchers are working to develop microbiome-based indices for diseases such as inflammatory bowel disease or obesity. Crowd-sourced studies such as the American Gut Project are working to expand and diversify microbiome datasets so that we can better understand the variability and begin to identify reproducible microbiome signatures. The microbiome data are extremely multidimensional and complex. Therefore, developing predictive patterns will likely require analyses of millions of samples linked to highly granular clinical metadata. Microbiome-based tests have potential to transform clinical care and become incorporated into the personalized medicine paradigm. However, we are at the very beginning of understanding what one's microbiome profile means for their susceptibility to or progression of disease. As patients approach their health care providers with requests to order commercial microbiome-based tests or to help interpret a report, it is important to set the expectation that these tests are not well suited for diagnoses of infectious diseases or validated in specific diagnoses of any diseases. There are far more unknowns than knowns regarding the role of the microbiome and human health.

For those interested in learning more on this topic, I will be discussing it at the 2019 Gut Microbiota for Health World Summit with my colleague Diane Hoffmann, JD, MS, from the University of Maryland School of Law. The AGA Center for Gut Microbiome Research and Education's scientific advisory board, on which Diane and I both serve, has also recognized the need for additional guidance. I would encourage my gastroenterology colleagues to continue sharing their experiences with microbiome-based tests through the AGA Community platform.

Dr. Khoruts, of the University of Minnesota, is a member of the AGA Center for Gut Microbiome Research & Education scientific advisory board.

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Recommended reading

- Staley C, Kaiser T, Khoruts A. Clinician guide to microbiome testing. Dig Dis Sci. 2018 Sep 28. doi: 10.1007/s10620-018-5299-6.
- Allaband C, McDonald D, Vazquez-Baeza Y, Minich JJ, Tripathi A, Brenner DA, et al. Microbiome 101: Studying, analyzing, and interpreting gut microbiome data for clinicians. Clin Gastroenterol Hepatol 2018. doi: 10.1016/j.cgh.2018.09.017.
- Costello EK, Stagaman K, Dethlefsen L, Bohannan BJ, Relman DA. The application of ecological theory toward an understanding of the human microbiome. Science. 2012. doi: 10.1126/science.1224203. Epub 2012 Jun 6.

Combination therapy is the key

Thiopurine *from page 1*

of patients with steroid-intractable CD; however, results showed only marginal benefit when using these agents alone. Subsequently, combination trials were performed, and these revealed modest efficacy for use as maintenance therapies in both UC and CD. Further studies reported that methotrexate is beneficial only as a maintenance therapy for CD given that trial evidence confirmed treatment limitations in patients with UC.

"Thiopurines also have the potential to reduce postoperative recurrence of [CD], in particular when administered with imidazole antibiotics," the experts wrote.

Despite its limitations in UC, 25 mg of methotrexate administered intramuscularly once weekly in combination with oral steroids has shown benefits for inducing disease remission and limiting steroid use in the management of active CD. Other trials have failed to show the same benefits with oral methotrexate. In addition, a number of clinical case series have reported benefit for use of methotrexate as a maintenance therapy for CD in patients who initially responded to methotrexate induction therapy.

Consequently, Dr. Hanauer and his colleagues recommended that methotrexate be given only in combination with biologics if being used for the treatment of UC.

"Thiopurines and methotrexate can be used in combination with anti-TNF biologics, in particular infliximab, to reduce immunogenicity and increase blood levels," they stated.

One agent in particular, thioguanine, exhibits unique therapeutic efficacy in patients allergic to azathioprine or mercaptopurine. Despite this benefit, thioguanine use has been linked with an increased risk of developing hepatic nodular regenerative hyperplasia, as well as venoocclusive disease. Given these limitations, long-term use of thioguanine was not recommended.

With respect to safety, routine laboratory monitoring for both liver and hematologic adverse effects is recommended. In rare cases, patients may develop secondary lymphomas in response to thiopurine treatment. Moreover, regular follow-up is essential because of the higher prevalence of nonmelanoma skin cancers seen with thiopurines use.

"Patients using thiopurines for the treatment of IBD ... should avoid excessive sun exposure and use high-strength sun block," the experts wrote. "Health care deliverers should ensure patients undergo appropriate dermatologic evaluations and investigate suspicious skin lesions in these patients," they further reported.

Another important consideration is ongoing infection risk, in particular with opportunistic and viral pathogens. Because of the immunosuppressive effects of therapy, both methotrexate and thiopurine use are linked with a greater chance of these infections. Dr. Hanauer and his colleagues recommended that, before initiation of these therapies, applicable preventative measures should be taken, including administration of influenza, human papillomavirus, varicella zoster virus, pneumococcus, and hepatitis B vaccines.

The experts went on to report that withdrawal of thiopurine agents,

Continued on following page

We want them to work

Probiotic *from page 1*

troenteritis treated in the United States or Canada.

In one of the two trials, conducted at 10 U.S. pediatric emergency departments, a 5-day course of *L. rhamnosus* GG did not improve outcomes, versus placebo, according to investigators, led by David Schnadower, MD, of Cincinnati (Ohio) Children's Hospital Medical Center.

Results of the trial, which comprised 971 children aged 3 months to 4 years, sharply contrast with results of previous studies and meta-analyses suggesting probiotics do improve outcomes in children with acute gastroenteritis.

However, those studies were hampered by small sample sizes, lack of probiotic quality control, and endpoints "of questionable relevance," among other limitations, according to Dr. Schnadower and his coauthors.

"The rigor of our research design calls into question recommendations to use *L. rhamnosus* GG in the treatment of children with acute gastroenteritis," the authors said in their published report.

Moderate to severe gastroenteritis within 14 days of enrollment, the trial's primary endpoint, occurred in 11.8% of children who received the probiotic, and in 12.6% of those who received placebo ($P = .83$).

Diarrhea duration was similar, at 49.7 hours and 50.9 hours in the probiotic and placebo groups, respectively ($P = .26$). Likewise, there were no significant differences in duration of vomiting, day-care absenteeism, or rate of household transmission between the study arms, investigators reported.

In the Canadian trial, which was similar to the U.S. trial but conducted independently, a probiotic product containing *L. rhamnosus* R0011 and *L. helveticus* R0052 also showed no significant benefit over placebo in reducing incidence of moderate to severe gastroenteritis within 14 days of enrollment.

That endpoint occurred in 26.1% of children assigned to probiotics, and 24.7% assigned to placebo ($P = .72$). The trial comprised 886 children 3-48 months presenting to one of six pediatric emergency departments in Canada.

As in the U.S. trial, investigators said there were no significant differences in diarrhea duration, at 52.5 and 55.5 hours in the probiotic and placebo groups, respectively ($P = .31$). And there were no significant differences in duration of vomiting, unscheduled health care provider visits, or adverse events.

Both trials used a modified Vesikari scale symptom score of 9 or higher (range, 0-20) to define moderate to severe gastroenteritis.

Rather than focusing on a single symptom such as diarrhea, the modified Vesikari scale score shows a "constellation of symptoms" associated with gastroenteritis, according to the Canadian investigators, led by Stephen B. Freedman, MDCM, of the department of pediatrics at Alberta Children's Hospital and Research Institute, University of Calgary.

Although the use of composite measures has been questioned, the modified Vesikari scale is externally validated and produced consistent findings for individual symptoms, according to the authors.

Despite the findings, the conclusions about the particular probiotic product evaluated in the trial cannot be generalized to others in the market, according to Dr. Freedman and his colleagues. Other "large, well conducted trials have aroused similar concerns regarding the effectiveness of probiotics for other conditions," they added. "Nonetheless, there may be specific indications and populations that will benefit from alternative probiotic agents."

The U.S. study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, among other sources. Dr. Schnadower reported that he received grants from the NICHD and nonfinancial support from iHealth.

The Canadian study was supported by the Canadian Institutes of Health Research, among other sources. Dr. Freedman reported that he received nonfinancial support from Calgary Laboratory Services, Copan Italia, Lallemand Health Solutions, Luminex, and ProvLab Alberta, along with grants from the Canadian Institutes of Health Research and Alberta Children's Hospital Foundation.

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SOURCES: Schnadower D et al. N Engl J Med. 2018 Nov 22;379(21):2002-14; Freedman SB et al. N Engl J Med. 2018 Nov 22;379(21):2015-26.

AGA Resource
Visit the AGA GI Patient Center for information that you can share with your patients about probiotics: http://ow.ly/FnOl30mMNQb.

PERSPECTIVE

Other probiotics might have success

These two studies, which are large and well conducted, do not support use of probiotics that contain *Lactobacillus rhamnosus* for moderate to severe gastroenteritis in children, according to J. Thomas LaMont, MD.

"These negative trial data will be valuable to clinicians and professional bodies in making decisions regarding the use of either of these probiotic formulations in children with diarrhea," Dr. LaMont said in an editorial.

Recommendations to use probiotics to treat acute gastroenteritis, as published by some professional societies, rely largely on studies that were underpowered or had issues related to study design or choice of endpoint, Dr. LaMont cautioned.

That said, there are many other probiotic formulations beyond the two evaluated in these trials, he added. Other probiotic agents have different mechanisms of action and ability to colonize the bowel, compared with *L. rhamnosus,* and thus could be effective against infectious diarrhea in children.

A probiotic formula including *L. plantarum* significantly reduced the sepsis rate in healthy newborns in one recent placebo-controlled trial in India, he added. That probiotic strain can colonize the intestinal tract for extended periods, compared with other probiotics.

"With their low cost and minimal toxic effects, probiotics have potential for the treatment of a variety of gastrointestinal and other diseases, but rigorous trials such as those described in this [study] are required to determine any potential efficacy or effectiveness," Dr. LaMont concluded.

Dr. LaMont is with the division of gastroenterology, Beth Israel Deaconess Medical Center, Boston. He had no disclosures related to his editorial (N Engl J Med. 2018 Nov 22;379[21]:2076-7).

Continued from previous page

when used in combination therapy, has the potential to reduce therapeutic levels of infliximab and promote development of antidrug antibodies. However, the experts did not suggest a method to manage these complications. Further studies are needed to answer these and other remaining questions regarding thiopurine use in the setting of IBD.

The authors had no conflicts of interest.

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SOURCE: Hanauer SB et al. Gastroenterology. 2018 Sep 6. doi: 10.1053/j.gastro.2018.08.043.

FDA approves rifamycin for traveler's diarrhea

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has approved rifamycin (Aemcolo) for the treatment of traveler's diarrhea caused by noninvasive strains of *Escherichia coli*.

FDA approval was based on results of three clinical trials. The efficacy of rifamycin was shown in a trial of 264 adults with traveler's diarrhea in Guatemala and Mexico. Compared with placebo, rifamycin significantly reduced symptoms. The safety of rifamycin was illustrated in a pair of studies including 619 adults with traveler's diarrhea who took rifamycin orally for 3-4 days. The most common adverse events were headache and constipation.

Traveler's diarrhea is the most common travel-related illness, affecting 10%-40% of travelers. It can be caused by many pathogens, but bacteria in food or water is the most common source. High-risk areas include much of Asia, the Middle East, Mexico, Central and South America, and Africa.

Rifamycin was not effective in patients with diarrhea complicated by fever and/or bloody stool or caused by a pathogen other than *E. coli*.

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GI & HEPATOLOGY NEWS

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Less medication is better

PPI *from page 1*

was 90-day mortality. Secondary outcomes were clinically important events in the ICU, clinically important gastrointestinal bleeding in the ICU, infectious adverse events in the ICU, and days alive without the use of life support within the 90-day period.

One or more clinically important events occurred in 21.9% of patients in the pantoprazole group and in 22.6% of the placebo group (RR, 0.96; 95% CI, 0.83-1.11). In the pantoprazole group, 2.5% of patients had clinically important gastrointestinal bleeding, compared with 4.2% in the placebo group, Dr. Krag and her coauthors wrote.

The findings are similar to other recently published results, which showed "no significant differences ... in the rates of death or infectious complications between patients receiving placebo or no prophylaxis and those receiving proton pump inhibitors," the authors wrote.

Dr. Krag reported financial support from Innovation Fund Denmark, Ehrenreich's Foundation, and several other organizations.

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Key clinical point
Just over 31% of patients in the pantoprazole group and 30.4% in the placebo group had died at 90 days (relative risk, 1.02; 95% confidence interval, 0.91-1.13; *P* = .76).

SOURCE: Krag M et al. N Engl J Med. 2018 Dec 6. doi: 10.1056/NEJMoa1714919.

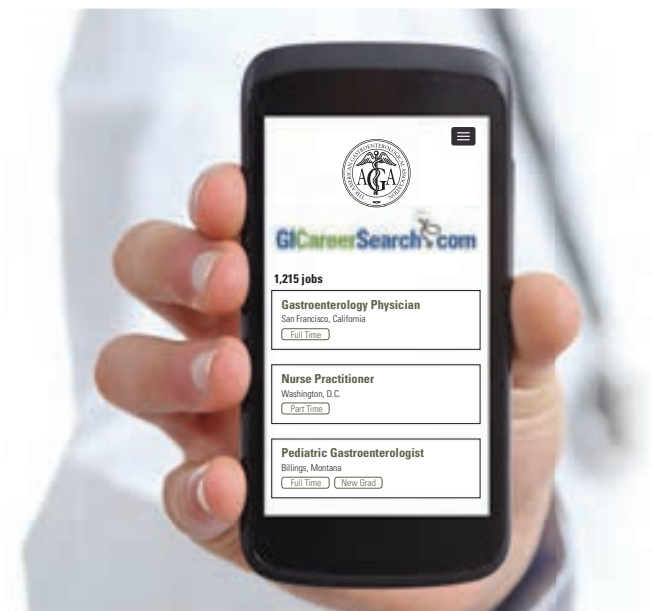
PERSPECTIVE

PPI should be reserved for the 'seriously ill'

"The take-home message from this trial is that, given the low incidence of clinically important upper gastrointestinal bleeding in the ICU, prophylaxis with a PPI [proton pump inhibitor], if initiated, should be reserved for seriously ill patients who are at high risk for this complication," wrote Alan Barkun, MD, CM, of McGill University, Montreal, and Marc Bardou, MD, PhD, of the Centre Hospitalier Universitaire Dijon–Bourgogne (France), in an editorial published with the study.

Though 90-day mortality was similar between groups in this trial, "the between-group difference in the rate of important upper gastrointestinal bleeding may still support the recommendation of using a prophylactic PPI" given the absence of a difference in the rate of adverse events between the two groups, they added.

Dr. Barkun reported no disclosures; Dr. Bardou reported support from the French Medicines Agency.



PERSPECTIVE

PPIs reduce GI bleeding risk but are not better than placebo for prophylaxis

Proton pump inhibitors (PPIs) are often used for prophylaxis in patients with a history of gastrointestinal bleeding (GIB) or at high risk for GIB due to concomitant dual-antiplatelet therapy. Two recently published studies investigated whether PPIs can mitigate the risk of GIB among patients in the intensive care unit and those using anticoagulation.

Dr. Krag and colleagues found no significant difference in the prophylactic effects of a single daily dose of intravenous pantoprazole compared with placebo to reduce the risk of death among ICU patients with at least one risk factor for GIB. There were numerically fewer GIB events that occurred in the group receiving PPI, but this was not significant. The pragmatic design did not mandate endoscopy in all patients and researchers did not control for enteral feeding, which could influence outcomes.

Based on these findings, routine prophylaxis with PPI in the ICU should not be universally recommended. Practically, many patients receive histamine$_2$ receptor antagonists for this indication. However, given the differential rates of bleeding between the groups, PPIs may be best reserved for patients at highest risk of GIB. Efforts should therefore be focused on defining the group that is most likely to benefit from PPI use.

In a retrospective cohort study of Medicare beneficiaries on anticoagulation, Dr. Ray and colleagues found that apixaban was associated with the lowest – and rivaroxaban the highest – risk for hospitalizations for upper GIB. Across all studied medications, this risk was significantly reduced when given with PPI cotherapy.

This study largely affirms prior findings on the relative risk profiles of anticoagulants for GIB, but given its retrospective nature, the effect of concomitant aspirin and nonsteroidal anti-inflammatory drugs could not be excluded. These findings suggest PPIs can reduce the risk of hospitalizations for GIB in this population and may have the greatest impact for those at highest baseline risk.

Together, these studies highlight the potential benefits of PPIs to prevent clinically important GIB in high-risk groups, but identifying patients with the best chance of deriving benefit from PPIs remains a challenge and should be a focus of future work.

David A. Leiman, MD, MSHP, is assistant professor of medicine, division of gastroenterology, Duke University Medical Center, Duke Clinical Research Institute, Durham, N.C. He has no conflicts of interest.

GI bleed: Anticoagulant choice, PPI cotherapy affect risk

BY JEFF CRAVEN
MDedge News

Patients receiving oral anticoagulant treatment had the lowest risk of gastrointestinal bleeding when taking apixaban, compared with rivaroxaban, dabigatran, and warfarin, according to a recent study.

Further, patients who received proton pump inhibitor (PPI) cotherapy had a lower overall risk of gastrointestinal bleeding, according to Wayne A. Ray, PhD, from the department of health policy at Vanderbilt University, Nashville, Tenn., and his colleagues.

"These findings indicate the potential benefits of a gastrointestinal bleeding risk assessment before initiating anticoagulant treatment," Dr. Ray and his colleagues wrote in their study, which was published in JAMA.

Dr. Ray and his colleagues performed a retrospective, population-based study of 1,643,123 Medicare beneficiaries (mean age, 76.4 years) who received 1,713,183 new episodes of oral anticoagulant treatment between January 2011 and September 2015. They analyzed how patients reacted to apixaban, dabigatran, rivaroxaban, or warfarin both with and without PPI cotherapy.

Overall, the risk of gastrointestinal bleeding across 754,389 person-years without PPI therapy was 115 per 10,000 person-years (95% confidence interval, 112-118) in 7,119 patients. The researchers found the risk of gastrointestinal bleeding was highest in patients taking rivaroxaban (1,278 patients; 144 per 10,000 person-years; 95% CI, 136-152) and lowest when taking apixaban (279 patients; 120 per 10,000 person-years; incidence rate ratio, 1,97; 95% CI, 1.73-2.25), compared with dabigatran (629 patients; 120 per 10,000 person-years; IRR, 1.19; 95% CI, 1.08-1.32) and warfarin (4,933 patients; 113 per 10,000 person-years; IRR, 1.27; 95% CI, 1.19-1.35). There was a significantly lower incidence of gastrointestinal bleeding for apixaban, compared with warfarin (IRR, 0.64; 95% CI, 0.57-0.73) and dabigatran (IRR, 0.61; 95% CI, 0.52-0.70).

There was a lower overall incidence of gastrointestinal bleeding when receiving PPI cotherapy (264,447 person-years; 76 per 10,000 person-years), compared with patients who received anticoagulant treatment without PPI cotherapy (IRR, 0.66; 95% CI, 0.62-0.69). This reduced incidence of gastrointestinal bleeding was also seen in patients receiving PPI cotherapy and taking apixaban (IRR, 0.66; 95% CI, 0.52-0.85), dabigatran (IRR, 0.49; 95% CI, 0.41-0.59), rivaroxaban (IRR, 0.75; 95% CI, 0.68-0.84), and warfarin (IRR, 0.65; 95% CI, 0.62-0.69).

The researchers noted that limitations in this study included potential misclassification of anticoagulant treatment, PPI cotherapy, and NSAIDs because of a reliance on filled prescription data; confounding by unmeasured factors such as aspirin exposure or *Helicobacter pylori* infection; and gastrointestinal bleeding being measured using a disease risk score.

This study was supported by a grant from the National Heart, Lung, and Blood Institute. The authors reported no relevant conflicts of interest.

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SOURCE: Ray WA et al. JAMA. 2018 Dec 4. doi: 10.1001/jama.2018.17242.

AGA CLINICAL PRACTICE UPDATE

Endoscopic submucosal dissection

BY CALEB RANS
MDedge News

The surgical technique endoscopic submucosal dissection (ESD) is a safe and appropriate option for the complete resection of large, early-stage, malignant gastric lesions, according to a new clinical practice update from the American Gastroenterological Association published in Clinical Gastroenterology and Hepatology.

Clinicians should recognize ESD as one of the main treatment modalities for GI cancer enclosed within the superficial esophageal mucosa, which includes squamous cell dysplasia, wrote Peter V. Draganov, MD, AGAF of the University of Florida in Gainesville with his fellow experts.

Endoscopic resection is a surgical method used to treat both malignant and nonmalignant GI lesions. Over the past several years, the technique has advanced significantly, progressing from snare polypectomy to endoscopic mucosal resection, with current practice now ESD. The minimally invasive technique is considered first-line therapy in patients with colorectal lesions lacking invasive cancer.

While the technique is widely used in Asian countries, and as practice continues to rise throughout Europe, uptake in the United States has been slow. Several factors may be responsible for this delay, including a lack of ESD experts and training centers, underestimation of the benefits associated with ESD, and a likely bias of American oncologists toward treatment with surgical resection. In recent years, extensive improvements have occurred in ESD technique, such as incorporation of pocket and tunnel strategies, which have significantly contributed to the overall safety and efficacy of the procedure.

"With low thresholds for performing endoscopy for upper GI symptoms and the promotion of screening colonoscopy for colon cancer prevention, more precancerous lesions and early cancers are being detected that may be amenable to endoscopic resection by ESD," the experts wrote.

For mucosal lesions too large to be removed by standard endoscopic resection, or lesions at high risk of being deemed malignant, the guidelines recommend using ESD to remove these lesions. Dr. Draganov and his colleagues acknowledged that the probability of lymph node metastasis is marginally higher when the procedure is used for these widened indications; however, the risk of metastasis remains sufficiently low. Along those lines, several additional recommendations were made related to the expanded indications for ESD, including use in certain patients with Barrett's esophagus, colorectal neoplasia, and other forms of superficial gastric cancer.

"Expanded indications for gastric ESD include moderately and well-differentiated superficial cancers that are [more than] 2 cm, lesions [up to] 3 cm with ulceration or that contain early submucosal invasion, and poorly differentiated superficial cancers [up to] 2 cm in size," the experts stated.

With respect to cost, endoscopic resection was found to provide significant savings in comparison to surgical techniques for the removal of colorectal lesions. The economic analysis revealed that using a lesion-specific ESD model for high-risk patients could allow for notable cost reductions.

"Although some insurers have begun preapproving and covering their members who might benefit from ESD, the hurdles preventing other patients from being covered for this innovative and potentially cost-saving procedure should be removed," they added.

Other recommendations were made in regards to effective implementation of a stepwise ESD educational model to train American endoscopists on how to properly perform the procedure. The proposed strategy involves completion of a formal training program, independent study, self-practice using animal models, and live viewing of cases by ESD experts. In addition, they recommend that newly trained endoscopists complete their first procedures on patients with absolute indications for ESD.

"At present, there is no standardized approach for ESD training in the United States," the experts wrote. They further explained that "the usual starting point is to attend an ESD course or series of courses that provide increasingly more in-depth exposure." And they concluded, "a guiding principle should be that our patients' interests and welfare stand above all else and that patients must not be used as an opportunity for practice or skills acquisition."

The practice update also recommends that endoscopists avoid the use of techniques that have the ability to produce submucosal fibrosis. Dr. Draganov and his colleagues warn that these practices, such as "tattooing in close proximity to or beneath a lesion for marking" and "partial snare resection of a portion of a lesion for histopathology," can impede subsequent endoscopic procedures.

Dr. Draganov and several coauthors disclosed financial affiliations with AbbVie, Boston Scientific, Cook Medical, Olympus America, and others.

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SOURCE: Draganov PV et al. Clin Gastroenterol Hepatol. 2018 Aug 2. doi: 10.1016/j.cgh.2018.07.041.

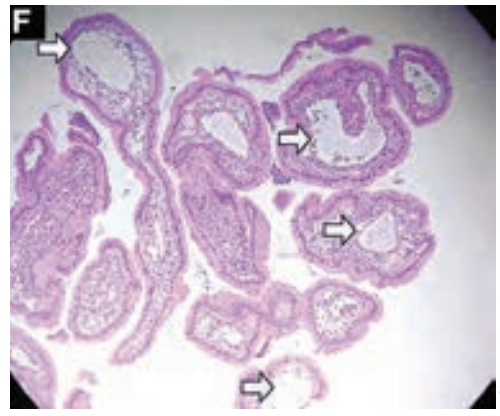
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 9: Primary intestinal lymphangiectasia

Histologic examination shows chronic inflammation of the ileum characterized by increased lymphoplasma cell infiltration of lamina propria without malignancy. Moreover, marked dilatation of lymphatic ducts that involved the mucosa was identified (Figure F, arrows; stain: hematoxylin and eosin; original magnification, ×100). On the basis of pathologic examinations, a diagnosis of primary intestinal lymphangiectasia (PIL) was made.

PIL is an extremely rare cause of protein-losing enteropathy characterized by the presence of dilated lymphatic channels in the mucosa, submucosa, or subserosa leading to protein-losing enteropathy.[1] The true incidence and prevalence of this disease remains unclear. The disease affects males and females equally, and usually occurs in children and young adults. To date, less than 200 cases of PIL have been reported in the literature. The clinical manifestations of PIL may be asymptomatic or symptomatic such as abdominal pain, edema, diarrhea, and dyspnea. The diagnosis is based on the typical endoscopic findings of diffuse scattered mucosal white blebs with characteristic histologic findings of abnormal lymphatic dilatation. Double-balloon enteroscopy and capsule endoscopy are powerful modalities to evaluate the entire affected area of PIL.[2] Although diet modification is a major treatment of PIL, several medicines have been reported to be useful such as corticosteroids, octreotide, and antiplasmin.[3] Moreover, in patients with segmental lesions, surgery with local bowel resection is a useful treatment.[3] In addition, PIL had a 5% risk of malignant transformation into lymphoma.[3]



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References

1. Waldmann TA, Steinfeld JL, Dutcher TF, et al. The role of the gastrointestinal system in "idiopathic hypoproteinemia." Gastroenterology. 1961;41:197-207.

2. Oh TG, Chung JW, Kim HM, et al. Primary intestinal lymphangiectasia diagnosed by capsule endoscopy and double balloon enteroscopy. World J Gastrointest Endosc. 2011;3:235-40.

3. Wen J, Tang Q, Wu, J. Primary intestinal lymphangiectasia: four case reports and a review of the literature. Dig Dis Sci. 2010;55:3466-72.

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Medicaid patients have higher MELD scores at time of liver transplantation

Key clinical point
Among patients without HCC, those with Medicaid coverage were 2.45 times more likely to have higher MELD scores at wait-list registration, compared with those covered by commercial or private insurance (*P* less than .01).

BY DOUG BRUNK
MDedge News

SAN FRANCISCO – Despite implementation of the Model for End Stage Liver Disease score to prioritize liver transplantation, patients with Medicaid have significantly higher MELD scores at the time of liver transplantation wait-list registration and at the time of transplantation, results from a study of national data found.

"It can be difficult for patients with Medicaid to access liver transplantation," lead study author Ann Robinson, MD, said in an interview at the annual meeting of the American Association for the Study of Liver Diseases. "These patients may be living in underserved areas with limited resources."

In an effort to evaluate insurance-specific disparities in severity of liver disease at the time of liver transplantation wait-list registration and at the time of liver transplantation, Dr. Robinson and her colleagues retrospectively evaluated the 2005-2016 United Network for Organ Sharing/Organ Procurement and Transplant Network liver transplant registry. They used multivariate linear regression models to make insurance-specific comparisons of MELD scores at wait-list registration and at liver transplantation, which included adjustments for age, sex, year, etiology of liver disease, body mass index, ascites, hepatocellular carcinoma (HCC), and hepatic encephalopathy.

Multivariate regression analysis revealed that, among patients without hepatocellular carcinoma, those with coverage other than private or commercial insurance had significantly higher MELD scores at wait-list registration.

Dr. Robinson, who is a third-year internal medicine resident at Highland Hospital, Oakland, Calif., reported findings from 88,542 liver transplantation wait-list registrants with a mean age of 56 years. Their overall mean MELD score was 17.4 at wait-list registration and 22.6 at time of liver transplantation. The greatest mean MELD score at the time of wait-list registration was observed in Medicaid patients (18.4, compared with 17.2 among Veterans Affairs patients, 17 among Medicare patients, and 17 among privately/commercially insured patients; *P* less than .01). Meanwhile, the greatest mean MELD score at the time of liver transplantation was observed in Medicaid patients (23.5, compared with 21.4 among VA patients, 21.3 among privately/commercially insured patients, and 21.1 among Medicare patients; *P* less than .01).

Multivariate regression analysis revealed that, among patients without hepatocellular carcinoma, those with coverage other than private or commercial insurance had significantly higher MELD scores at wait-list registration (*P* less than .01). Specifically, the odds ratio was highest for VA patients (odds ratio, 2.59), followed by those covered by Medicaid (OR, 2.45) and Medicare (OR, 1.86). Similar trends were observed in hepatocellular carcinoma patients, with the highest biological MELD score at wait-list seen in those covered by Medicaid.

On regression analysis, while Medicaid patients with hepatocellular carcinoma had significantly higher biological MELD scores at time of liver transplantation, compared with those with private/commercial insurance (Medicaid OR, 2.06; *P* less than .05), no differences were observed among patients without hepatocellular carcinoma.

Dr. Robinson reported having no financial disclosures.

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SOURCE: Robinson A et al. Hepatology. 2018 Oct 1;68(S1), Abstract 464.

DDSEP eight

Quick quiz answers

Q1. CORRECT ANSWER: C

Rationale
AIDS cholangiopathy is uncommon in the Western world, but it can be encountered among patients with untreated HIV who are severely immunosuppressed (CD4 count typically les than 100/mm^3). The presence of papillary stenosis and sclerosing cholangitis is unique to AIDS cholangiopathy, and is the most common cholangiographic manifestation. Among the organisms listed, Cryptosporidium is the most commonly isolated pathogen associated with AIDS cholangiopathy. Nearly 30% of HIV-positive patients in the infamous 1993 Milwaukee cryptosporidiosis outbreak reported biliary symptoms. The presence of diarrhea may be the initial clinical manifestation. For example, biliary tract disease developed in approximately 20% of HIV-positive patients with diarrhea secondary to *C. parvum*. Cytomegalovirus has been frequently reported in AIDS cholangiopathy, as have multiple other pathogens (to a lesser degree) including Cyclospora, various Microsporidia, and Mycobacterium species. *Ascaris lumbricoides* can cause infestations of the biliary tree but it has not been implicated in AIDS cholangiopathy.

References

1. Tonolini M, Bianco R. HIV-related/AIDS cholangiopathy: pictorial review with emphasis on MRCP findings and differential diagnosis. Clin Imaging. 2013;37:219-26.
2. Hashmey R, Smith NH, Cron S, et al. Cryptosporidiosis in Houston, Texas. A report of 95 cases. Medicine. 1997;76:118-39.
3. Forbes A, Blanshard C, Gazzard B. Natural history of AIDS related sclerosing cholangitis: a study of 20 cases. Gut. 1993;34:116-21.

Q2. CORRECT ANSWER: A

Rationale
Anti-TNF therapy is relatively safe and well tolerated. However, there are a few important issues to consider prior to initiation of therapy. There is a risk of reactivation of both *Mycobacterium tuberculosis* and hepatitis B. In this patient's case, her PPD positivity is likely a false positive from remote BCG vaccination. An interferon gamma release assay (e.g. QuantiFERON®) can be checked to confirm this; even if that is positive, in the absence of active tuberculosis, she can be treated for latent TB for several weeks prior to initiation of anti-TNF therapy. Her hepatitis B serologies do not suggest chronic infection but rather prior infection with resolution. In this case, anti-TNF therapy is not precluded; rather, the AGA recommends considering concurrent antiviral prophylaxis while on anti-TNF therapy. Anti-TNF agents are not known to significantly increase the risk of progressive multifocal leukoencephalopathy like the nonselective anti-integrin natalizumab, so JC virus antibody positivity does not preclude their use. There is a slight increased risk of melanoma in those on anti-TNF therapy; nonmelanoma skin cancers are of greater concern in those on thiopurine therapy. Finally, anti-TNF therapy should be avoided in those with demyelinating diseases or those at high risk for such diseases.

References

1. Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2014;148(1):215-9.
2. Long MD, Martin CF, Pipkin CA, et al. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology. 2012;143(2):390-9.
3. Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: A meta-analysis. Am J Gastroenterol. 2014;109:163-9.

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Skin rashes often accompany drug-induced liver injury

BY JIM KLING
MDedge News

SAN FRANCISCO – More than a quarter of drug-induced liver injury (DILI) cases also involve skin reactions, most often drug rash with eosinophilia and system symptoms (DRESS) syndrome. These dual cases of DILI and drug-induced skin injury (DISI) underscore the need for hepatologists to pay attention to dermatologic conditions and emphasize the need for the two specialties to work together.

The findings suggest that DISI/DILI comorbidity is not uncommon, and may hint at underlying mechanisms that could be used to tailor treatment, according to Harshad Devarbhavi, MD, who presented the study at the annual meeting of the American Association for the Study of Liver Diseases. "My message was that people should work more and see if there's any type of genotype or HLA [human leukocyte antigen] that produces this reaction. It's a multisystem disease. It doesn't belong to dermatologists; it's a domain that also belongs to hepatologists," said Dr. Devarbhavi, who is a hepatology fellow at St. John's Medical College in Bangalore, India.

Of DILI/DISI and Stevens-Johnson syndrome/toxic epidermal necrolysis cases, 75% were associated with four drug classes: antiepileptic drugs, dapsone, antiretroviral therapies, and leflunomide.

DISI is more common than DILI, and may or may not be caused by an immune response. The two conditions were previously known to co-occur, but it is rarely reported because dermatologists and hepatologists report findings in different journals.

The researchers defined DILI as a fivefold or greater increase in aspartate aminotransferase or alanine aminotransferase; a threefold or greater increase with symptoms, including cutaneous reactions; any elevation of AST, ALT, or alkaline phosphatase accompanying a bilirubin increase of 2 mg/dL or more; or a twofold or higher increase in ALP combined with a cutaneous reaction.

They analyzed 921 DILI patients from a single registry in India, who were seen between 1997 and April 2018. All patients with skin reactions were seen by dermatologists and competing causes were excluded. A total of 28% of patients with DILI also had DISI, 13% of whom were also HIV positive; 56% developed jaundice. The mean age of patients with DILI/DISI was 35 years, compared with 42 years in DILI only patients (P = .001), and the mean duration of drug therapy was 42 days, compared with 89 days (P = .002). Twelve percent of DILI/DISI patients died, which was lower than the 17% mortality in those with DILI alone.

Of the DILI/DISI patients, 59% experienced DRESS, and 19% had Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Six percent of patients with DRESS died, as did 22% of those with SJS/TEN. Mortality was 16% among those with other skin manifestations. Eighteen percent of those with jaundice died, compared with 3% of those without jaundice.

Thirty patients with DILI/DISI died; 37% (11) of them had SJS/TEN, compared with 17% of survivors (P = .01). DRESS was more common in survivors (62% vs. 33%; P = .02).

Of DILI/DISI and SJS/TEN cases, 75% were associated with four drug classes: antiepileptic drugs, dapsone, antiretroviral therapies, and leflunomide.

"The liver is the biggest internal organ in the body, and skin is the largest external organ, so there is some correlation between the two, but people haven't looked at it. People should come together and see why some drugs produce both these injuries. I think there is some mechanistic information in these drugs," said Dr. Devarbhavi.

No source of funding was disclosed. Dr. Devarbhavi disclosed no relevant conflicts.

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SOURCE: Devarbhavi H et al. Hepatology. 2018 Oct 1;68(S1), Abstract 37.

Weight loss meds may have role after bariatric surgery

BY KARI OAKES
MDedge News

NASHVILLE – Is there a role for weight loss medications to help manage weight regain after bariatric surgery? Perhaps, according to a recent analysis of single-center clinical data.

Phentermine and topiramate were each prescribed to between 10% and 12.5% of bariatric surgery patients at Boston Medical Center in recent years. That figure had been steadily increasing since 2004, when data collection began, Nawfal W. Istfan, MD, PhD, said at the meeting presented by the Obesity Society and the American Society for Metabolic and Bariatric Surgery.

However, the center didn't know how patients who had received medication fared for long-term maintenance of weight loss, compared with those who had surgery alone; also, there were no clinical guidelines for prescribing weight loss medications (WLMs). "Have we done those patients any benefit by prescribing weight loss medications after gastric bypass surgery?" asked Dr. Istfan. The answer from the Boston Medical Center data is a qualified "yes"; patients with the highest rates of weight regain who were adherent to their medication did see lower rates of regain, and fewer rapid weight regain events.

Comparing patients who received prescriptions with those who did not, patients with less weight loss at nadir were more likely to receive a prescription. "This could very well be the reason they were prescribed a medication: They did not lose as much weight, and they are more likely to ask us" for WLMs, said Dr. Istfan, an endocrinologist at Boston University. However, for those who were prescribed WLMs, the slope of regain was flatter than for those who didn't receive medication. Of the 626 patients included in the study, 91 received phentermine alone, 54 topiramate alone, and 113 both phentermine and topiramate. Three received lorcaserin.

Those receiving medication were similar to the total bariatric surgery population in terms of age, sex, comorbidities, socioeconomic status, and preoperative body mass index, said Dr. Istfan, the senior author in the study. However, Hispanic individuals were more likely to receive WLMs, he said.

Recognizing that "the ratio of weight regain to nadir weight is more indicative of overfeeding than other parameters," Dr. Istfan said that he and his colleagues divided patients into quartiles of regain, based on this ratio. The quartiles fell out so that those who had the least regain either lost weight or regained less than 1.4%, to make up the first quartile. The second quartile included those who regained from 1.5% to 6.26%, while the third quartile ranged up to 14.29% regain. Those who regained 14.3% or more were in the highest quartile of weight regain.

KARI OAKES/MDEDGE NEWS

Dr. Nawfal W. Istfan asked whether prescribing weight loss medications after gastric bypass surgery has provided any benefit.

As for characteristics of the quartiles, there were more African Americans in the two higher quartiles (P = .017). More patients had achieved maximal weight loss in the highest quartile of regain (P less than .0001), though preoperative BMI had also been higher in this group (P = .0008).

After statistical adjustment, the investigators found that, for individuals who had the highest quartile of regain, patients who were adherent to their WLMs had significantly less weight regain than those who took no medication (P = .014). However, patients considered nonadherent saw no medication effect on weight regain. The differences were small overall, with adherent patients regaining about 27% of weight relative to their nadir and those who didn't take WLMs regaining about 30%. These significant results were seen long after bariatric surgery, at about 7 years post surgery.

In another analysis that looked just at the quartile of patients with the highest regain rate, weight regain was significantly delayed among those who were prescribed – and were adherent to – WLMs (P = .023). The analysis used a threshold weight regain rate of 1.22% per month; levels lower than that did not see a significant drug effect, and the effect was not seen for those not adherent to their WLMs.

Finally, an adjusted statistical analysis compared those taking and not taking WLMs to see whether WLMs were effective at preventing weight regain in rolling 90-day intervals throughout the study period. Again, in the highest quartile, those who were adherent to WLMs had a lower odds ratio of hitting the 1.22%/month regain rate, compared with those not taking medication (OR, 0.570; 95% confidence interval, 0.371-0.877; P = .01). The effect was not significant for the nonadherent group (OR, 0.872; 95% CI, 0.593-1.284; P = .489).

As more bariatric procedures are being done, and as more patients are living with their surgeries, physicians are seeing more weight regain, said Dr. Istfan, noting that it's important to assess efficacy of WLMs in the postsurgical population. "Recent work showed that, by 5 years after gastric bypass, half of patients had regained more than 15% of their nadir weight, and two-thirds of patients had regained more than 20% of their total maximum weight loss, said Dr. Istfan (King WC et al. JAMA. 2018;320:1560).

Typically, patients will see about a 35% weight loss at their nadir, with a gradual increase in weight gain beginning about 2 years after surgery. Though it's true that a net weight loss of 25% is still good, it can be a misleading way to look at the data, "because it does not focus on the process of weight regain itself," said Dr. Istfan.

"Despite the maintenance of substantial weight loss, weight regain is concerning: It's the present and future, not the past," he said.

Regaining weight necessarily means that patients are having excess nutrient intake and a net-positive energy balance; this state can be associated with oxidative stress, inflammation, and insulin resistance – all potential contributors to the recurrence of comorbidities.

What's to be done about weight regain, if it's a point of concern? One option, said Dr. Istfan, is to consider more surgery. Patients might want a "re-do"; techniques that have been tried include reshaping the pouch and doing an anastomosis plication. If a gastro-gastric fistula's developed, that can be corrected, he said.

Some factors influencing regain can be targeted by behavioral therapy. These include addressing alcohol consumption, discouraging grazing, encouraging exercise, and assessing and modifying diet quality in general.

"There is a general reluctance on the part of physicians to use weight loss medications after bariatric surgery," said Dr. Istfan. Reasons can include concern about further nutritional compromise, especially when thinking about long-term use of appetite-suppressing medications. Importantly, there aren't clinical guidelines for prescribing WLMs after bariatric surgery, nor is there a strong body of prospective studies in this area.

Dr. Istfan noted that the medical and surgical bariatric teams collaborate closely at Boston Medical Center to provide pre- and postoperative assessment and management.

The long observational interval and ethnic and socioeconomic diversity of the study population are strengths, said Dr. Istfan. Also, the three different multivariable models converged to similar findings.

However, the study was retrospective, with some confounding likely, and each prescriber involved in the study may have varying prescribing practices. Also, adherence was assessed by follow-up medication appointments, a measure that likely introduced some inaccuracy.

"Weight loss medications are potentially effective tools to counter weight regain after bariatric surgery; prospective studies are needed to optimize the use of weight loss medications after bariatric surgery," said Dr. Istfan.

Dr. Istfan reported no outside sources of funding, and no conflicts of interest.

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SOURCE: Anderson W et al. Obesity Week 2018, Abstract T-OR-2016.

AGA Resource

AGA provides GIs with a comprehensive, multidisciplinary process to guide and personalize innovative obesity care for safe and effective weight management. Learn more at http://ow.ly/fFA330mWKCn.

Part D proposal includes prior authorization, step therapy

BY GREGORY TWACHTMAN
MDedge News

Rules governing the six protected medication classes covered by Medicare Part D could change under a proposal that would allow for utilization management or potential formulary exclusion of a drug for price increases.

Currently, Medicare Part D prescription drug benefit plans must cover "all or substantially all" approved drugs in six classes (antidepressants, antipsychotics, anticonvulsants, antiretrovirals, and antineoplastics). The proposed rule would allow three exceptions aimed at giving plans more negotiating leverage to help lower prices.


MS. VERMA

Plans would be allowed to implement prior authorization and step therapy for protected-class drugs, "including to determine use for a protected class indication," according to a fact sheet. They also could exclude a protected-class drug from their formulary "if the drug represents only a new formulation of an existing single-source drug or biological product, regardless of whether the older formulation remains on the market."

This does not change requirements that at least two drugs per class be covered, Seema Verma, administrator of the Centers for Medicare & Medicaid Services, said at a briefing. "In some classes, there are lots of competitors. For example, for antidepressants, there are lots of new generics available, so we see plans being in a very strengthened negotiating position. But in other classes, where there may not be as many drugs that are available, you might not see the same type of step therapy and prior authorization because there are just not that many options. It is really going to depend on the class of drugs and what's available and the plans' ability to negotiate discounts with manufacturers."

Plans could exclude a protected-class drug if its price had increased greater than inflation, Ms. Verma said, but they could not use this to not cover any drugs in a class if available options are limited to one or two drugs.

"Foremost in our minds was the impact on patients and ensuring affordability and access to prescription drugs," Ms. Verma said.

Oncologists don't seem to agree.

"For the first time ever, Medicare patients with cancer and other serious diseases [who] rely on drugs in these protected therapeutic categories, will no longer have guaranteed access to potentially life-saving drugs. Instead, they will be subjected to 'fail first' step therapy and formulary restrictions that potentially restrict them from receiving the evidence-based therapies that their trained physicians prescribe as first-line cancer treatment," Jeff Vacirca, MD, president of the Community Oncology Alliance, said in a statement. "Step therapy requirements are driven by financial interests to save money and not by what is in the best medical interest of patients. Treatment decisions are made by nameless and faceless corporate bureaucrats who are often not board certified in the diseases they are making coverage decisions over."

AGA is concerned that these proposed changes will limit access for current and future beneficiaries and will add to the growing regulatory burden that physicians already face.

The proposal also would codify a policy implemented for 2019 that allows Medicare Advantage to implement step therapy tools for Part B drugs. And like the 2019 policy, the proposal would apply to new medication starts only, must be reviewed by a plan's pharmacy and therapeutics committee, and must have an expedited exceptions process.

The proposal also specifically allows pharmacists to advise Part D beneficiaries on lower-cost options – something current regulations prohibit – and would require Part D explanation of benefits forms to include drug pricing information and lower-cost therapeutic alternatives.

The proposal is part of a broader update for Medicare Parts C and D in 2020 issued by CMS. It was published online Nov. 26 and is scheduled for publication in the Federal Register on Nov. 30. Comments can be made at www.regulations.gov through Jan. 25, 2019.

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Facing a lawsuit? Take the right steps early

BY ALICIA GALLEGOS
MDedge News

It's happened. A patient is suing you. Now what? Legal experts warn that a doctor's first steps after a lawsuit can dramatically impact the outcome of the case – for better or worse.

Below, medical malpractice defense attorneys share the most important do's and don'ts for physicians after they receive a lawsuit notice. Spoiler: Whatever you do, don't ignore the summons.

• Do contact your insurer and/or risk manager. Once you receive notice of a lawsuit, the first step is calling your medical malpractice insurer and/or risk manager, said Steven Fitzer, a medical liability defense attorney based in Tacoma, Wash. The insurer and risk manager will take the matter from there and advise your next moves. Resist the urge to disregard the notice and hope that the challenge goes away when the patient is no longer angry, he said. Failing to notify the insurer in a timely manner could be a policy violation and affect current or future coverage.

• Don't contact the plaintiff/patient or patient's family. Instinctively, many physicians feel compelled to call the patient and attempt to settle the conflict verbally, particularly if they have had a long-standing relationship, Mr. Fitzer said in an interview. Don't do it.


MR. MORONEY

"In 42 years, I've never come across a physician who successfully talked somebody out of a lawsuit, once it was started," he said. "It's a pipe dream."

Keep in mind that conversations with patients after a lawsuit filing can be used against doctors in court and certain words can easily be misconstrued as admissions of guilt.

• Do secure all medical records pertaining to the case. Obtain and print copies of all information relevant to the patient's suit, such as history, billing records, letters, and medical chart. Store the data in a secure location in preparation for transferring to the insurer and/or attorney, said Michael Moroney, a medical liability defense attorney based in Teaneck, N.J.

• Don't access or change the record. It may seem tempting to review the plaintiff's medical record and fix any errors found. However, accessing the patient's electronic data can appear as an attempt to manipulate or delete relevant data, said Joshua R. Cohen, a medical liability defense attorney based in New York.


MR. COHEN

"Avoid accessing [the] EMR or PAC system [and] leaving a digital fingerprint," he said in an interview. "For example, if a radiologist is sued for an alleged failure to diagnose breast cancer, they should not open that study on their computer as an audit trail will show that. Worse is when they start making measurements after the lawsuit which are now discoverable as part of the lawsuit."

Leave the record alone and let the attorneys handle the data from here on out, he advised.

• Do discuss the patient case openly with your attorney and risk manager. Honesty about all aspects of a medical case from the start sets the right tone for a positive relationship between doctor and attorney, experts say. Help your attorney understand the medicine so that they can speak intelligently about the details to the court and any retained experts, Mr. Fitzer recommended. If disagreements continually arise among physicians and attorneys, and the match fails, consider speaking to the insurer about a change in attorneys.

• Don't discuss the case. As Mr. Fitzer puts it, "loose lips sink ships." Physicians lose confidentiality protections when they talk about lawsuit details with third parties, and those conversations could come back to haunt them. This includes colleagues and staff members in the patient's care loop, said Catherine Flynn, a medical liability defense attorney also based in Teaneck. The third parties could later be questioned by the plaintiff's attorney about the case, which could harm your defense.

"It's like that kid game of telephone where you may something to the nurses and then a year later, they're deposed, and their recollection is very different," Ms. Flynn said in an interview. "It turns into something that you did not say."


MS. FLYNN

Your spouse is the exception. Most states protect conversations among spouses and bar husbands and wives from having to testify against their spouse.

• Do alert staff to the lawsuit and track any document requests. Following a lawsuit notice, inform staff that a claim has been filed by a patient – without going into detail. Be alert to document requests by nonpatients and make sure your attorney is aware of such requests. For example, some plaintiffs hire a private investigator to contact the medical practice and attempt to obtain records, Mr. Moroney said. In other cases, the plaintiff's attorney or their paralegal tries to get copies of the medical chart or billing records.

• Don't release any patient data to third parties. Ensure that staff members do not provide any patient information to the plaintiff's attorney or other third parties, Mr. Moroney said. All relevant records should go through your attorney. No questions about the patient or the circumstances of the complaint should be divulged by the doctor or staff members to any third party, he said.

• Do seek emotional support from family and friends. Facing a lawsuit can be draining, both physically and mentally. Make time for self-care and lean on loved ones when needed, Mr. Fitzer said. Sharing your feelings – without going into detail about the case – can help relieve stress and reduce the emotional strain of being sued.

• Don't isolate yourself. "This can be an isolating experience," Mr. Fitzer said. "You need support. You need reinforcements. Take care of yourself and your family – they are your biggest source of support."

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Fewer insured may have helped slow health spending

BY GREGORY TWACHTMAN
MDedge News

Health care spending as a percentage of gross domestic product remained relatively stable in 2017, despite a slowdown in the growth of spending.

Total health care spending in the United States was $3.5 trillion in 2017, an increase of 3.9% from 2016, according to data released by the Centers for Medicare & Medicaid Services.

The growth rate was down from that of 2016 (4.8%) but similar to growth rates experienced during 2008-2013, according to a research article in Health Affairs.

"The slower growth in health care spending in 2017 resulted primarily from slower growth in hospital care, physician and clinical services, and retail prescription drugs, with residual use and intensity of these goods and services contributing substantially to the trend," Anne B. Martin, an economist in the CMS Office of the Actuary's National Health Statistics Group, and her colleagues wrote.

The report notes that slower growth in the use and intensity of health care goods and services in 2017 "may have been affected by slower growth in overall health insurance enrollment, as the insured share of the population fell from 91.1% in 2016 to 90.9% in 2017."

Spending on hospital care increased 4.6% to $1.1 trillion in 2017 and accounted for 33% of total health care spending; however, growth was slower than in the previous year (5.6%). Ms. Martin and her colleagues noted that growth in outpatient visits slowed while growth in inpatient days increased at about the same rate and prices in hospital care grew in 2017 to 1.7% from 1.2% in the previous year.

Spending on physician and clinical services grew 4.2% in 2017 to $694.3 billion and accounted for 20% of total health care spending. The growth rate is down from the previous year (5.6%) and a recent peak of 6% in 2015.

Spending on retail prescription drugs grew 0.4% in 2017 to $333.4 billion and accounted for 10% of total national health spending. It is the slowest growth rate increase since 2012, a year that saw a number of blockbuster drugs lose patent protection. This was down from a growth rate of 2.3% in 2016 and down from recent rates of 12.4% in 2014 and 8.9% in 2015.

"Slower growth in non-price factors, such as the use and mix of retail prescription drugs – and, to a lesser extent, in retail prescription drug prices – contributed to the slower overall growth in retail prescription drug spending in 2017," according to the authors. Key factors included slower growth in the number of prescriptions dispensed, the continued shift to lower-cost generics, and slower growth in the volume of high-cost drugs, particularly those used to treat hepatitis C.

Medicare spending, which represents 20% of all national health care spending in 2017 ($705.9 billion), grew 4.2%, a slight decline from the 4.3% growth in 2016. Enrollment growth slowed slightly to 2.5% in 2017 from 2.7% in the previous year, while in the same time frame, per-enrollee expenditures increased slightly to 1.7% from 1.6%. Slower growth in fee-for-service Medicare spending was offset by faster growth in spending by Medicare private health plans.

Medicaid spending reached $581.9 billion (17% of national health care spending), and the growth rate slowed for the third straight year, increasing 2.9% in 2017 versus 4.2% in 2016. The slower growth "was influenced by a deceleration in enrollment growth and a reduction in the Medicaid net cost of health insurance as the federal government recovered payments from managed care organizations based on their favorable prior-period experience," the authors stated.

Enrollment growth has been decelerating following a peak of growth of 11.9% in 2014 because of states that elected to expand Medicaid eligibility, which was followed by 3 years of slower growth rates of 4.9%, 3.0%, and 2.0% in 2015, 2016, and 2017, respectively. Per-enrollee spending also slowed to 0.9% growth in 2017 from a rate of 1.2% in 2016, attributed to "the decline in government administration and the net cost of insurance."

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PRACTICE MANAGEMENT TOOLBOX: Patient-reported outcomes for patients with chronic liver disease

BY ZOBAIR M. YOUNOSSI, MD, MPH, AGAF

Chronic liver disease (CLD) and its complications such as decompensated cirrhosis and hepatocellular carcinoma are major causes of mortality and morbidity worldwide.[1,2] In addition to its clinical impact, CLD causes impairment of health-related quality of life (HRQL) and other patient-reported outcomes (PROs).[1] Furthermore, patients with CLD use a substantial amount of health care resources, making CLD responsible for tremendous economic burden to the society.[1,2]

Although CLD encompasses a number of liver diseases, globally, hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as alcoholic and nonalcoholic steatohepatitis (NASH), are the most important causes of liver disease.[1,2] In this context, recently developed treatment of HBV and HCV are highly effective. In contrast, there is no effective treatment for NASH and treatment of alcoholic steatohepatitis remains suboptimal.[3] In the context of the growing burden of obesity and diabetes, the prevalence of NASH and its related complications are expected to grow.[4]

In recent years, a comprehensive approach to assessing the full burden of chronic diseases such as CLD has become increasingly recognized. In this context, it is important to evaluate not only the clinical burden of CLD (survival and mortality) but also its economic burden and its impact on PROs. PROs are defined as reports that come directly from the patient about their health without amendment or interpretation by a clinician or anyone else.[5,6] Therefore, this commentary focuses on reviewing the assessment and interpretation of PROs in CLD and why they are important in clinical practice.

Assessment of patient-reported outcomes

Although a number of PRO instruments are available, three different categories are most relevant for patients with CLD. In this context, PRO instruments can be divided into generic tools, disease-/condition-specific tools, or other instruments that specifically measure outcomes such as work or activity impairment (Table 1). Generic HRQL tools measure overall health and its impact on patients' quality of life. One of the most commonly used generic HRQL tools in liver disease is the Short Form-36 (SF-36) version 2. The SF-36 version 2 tool measures eight domains (scores, 0–100; with a higher score indicating less impairment) and provides two summary scores: one for physical functioning and one for mental health functioning. The SF-36 has been translated into multiple languages and provides age group– and disease-specific norms to use in comparison analysis.[7] In addition to the SF-36, the Sickness Impact Profile also has been used to assess a change in behavior as a consequence of illness. The Sickness Impact Profile consists of 136 items/12 categories covering activities of daily living (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behavior, emotional behavior, and communication). Items are scored on a numeric scale, with higher scores reflecting greater dysfunction as well as providing two aggregate scores: the psychosocial score, which is derived from four categories, and an aggregate physical score, which is calculated from three categories.[8] Although generic instruments capture patients' HRQL with different disease states (e.g., CLD vs. congestive heart failure), they may not have sufficient responsiveness to detect clinically important changes that can occur as a result of the natural history of disease or its treatment.[9]

DR. YOUNOSSI

For better responsiveness of HRQL instruments, disease-specific or condition-specific tools have been developed. These tools assess those aspects of HRQL that are related directly to the underlying disease. For patients with CLD, several tools have been developed and validated.[10-12] One of the more popular tools is the Chronic Liver Disease Questionnaire (CLDQ), which was developed and validated for patients with CLD.[10] The CLDQ has 29 items and 6 domains covering fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry.[10] More recently, HCV-specific and NASH-specific versions of the CLDQ have been developed and validated (CLDQ-HCV and CLDQ–nonalcoholic fatty liver disease [NAFLD]/NASH). The CLDQ-HCV instrument has some items from the original CLDQ with additional items specific to patients suffering from HCV. The CLDQ-HCV has 29 items that measure 4 domains: activity and energy, emotional, worry, and systemic, with high reliability and validity.[11] Finally, the CLDQ-NAFLD/NASH was developed in a similar fashion to the CLDQ and CLDQ-HCV. The CLDQ-NAFLD/NASH has 36 items grouped into 6 domains: abdominal symptoms, activity, emotional, fatigue, systemic symptoms, and worry.[12] All versions of the CLDQ are scored on a Likert scale of 1-7 nd domain scores are presented in the same manner. In addition, each version of the CLDQ can provide a total score, which also ranges from 1 to 7. In this context, the higher scores represent a better HRQL.[10-12]

Over the years, studies using these instruments have shown that patients with CLD suffer significant impairment in their PROs in all domains measured when compared with the population norms or with individuals without liver disease.

In addition to generic and disease-specific instruments, some investigators may elect to include other instruments that are designed specifically to capture fatigue, a very common symptom of CLD. These include the Functional Assessment of Chronic Illness Therapy-Fatigue, Fatigue Symptom Severity, and Fatigue Assessment Inventory.[13,14]

Finally, work productivity can be influenced profoundly by CLD and can be assessed by self-reports or questionnaires. One of these is the Work Productivity Activity Impairment: Specific Health Problem questionnaire, which evaluates impairment in patients' daily activities and work productivity associated with a specific health problem, and for patients with liver disease, patients are asked to think about how their disease state impacts their life. Higher impairment scores indicate a poorer health status and range from 0 to 1.[15] An important aspect of the PRO assessment that is utilized in economic analysis measures health utilities. Health utilities are measured directly (time-trade off) or indirectly (SF6D, EQ5D, Health Utility Index). These assessment are from 0 (death) to 1 (perfect health). Utility adjustments are used to combine qualty of life with quantity of life such as quality-adjusted years of life (QALY).[16]

Patient-reported outcome results for patients with chronic liver disease

Over the years, studies using these instruments have shown that patients with CLD suffer significant impairment in their PROs in all domains measured when compared with the population norms or with individuals without liver disease. Regardless of the cause of their CLD, patients with cirrhosis, especially with decompensated cirrhosis, have the most significant impairments.[16,17] On the other hand, there is substantial evidence that standard treatment for decompensated cirrhosis (i.e., liver transplantation) can significantly improve HRQL and other PROs in patients with advanced cirrhosis.[18]

In addition to the data for patients with advanced liver disease, there is a significant amount of PRO data that has been generated for patients with early liver disease. In this context, treatment of HCV with the new interferon-free direct antiviral agents results in substantial PRO gains during treatment and after achieving sustained virologic response.[19] In fact, these improvements in PROs have been captured by disease-specific, generic, fatigue-specific, and work productivi-

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ty instruments.[19]

In contrast to HCV, PRO data for patients with HBV are limited. Nevertheless, recent data have suggested that HBV patients who have viral suppression with a nucleoside/nucleotide analogue have a better HRQL.[20] Finally, PRO assessments in subjects with NASH are in their early stages. In this context, HRQL data from patients with NASH show significant impairment, which worsens with advanced liver disease.[21,22] In addition, preliminary data suggest that improvement of fibrosis with medication can lead to improvement of some aspects of PROs in NASH.[23,24]

Clinical practice and patient-reported outcomes

The first challenge in the implementation of PRO assessment in clinical practice is the appreciation and understanding of the practicing gastroenterologists and hepatologists about its importance and relevance to clinicians. Generally, clinicians are more focused on the classic markers of disease activity and severity (laboratory tests, and so forth), rather than those that measure patient experiences (PROs). Given that patient experience increasingly has become an important indicator of quality of care, this issue may become increasingly important in clinical practice. In addition, it is important to remember that PROs are the most important outcomes from the patient's perspective. Another challenge in implementation of PROs in clinical practice is to choose the correct validated tool and to implement PRO assessment during an office visit. In fact, completing long questionnaires takes time and resources, which may not be feasible for a busy clinic. Furthermore, these assessments are not reimbursed by payers, which leave the burden of the PRO assessment and counseling of patients about their interpretation to the clinicians or their clinical staff. Although the other challenges are easier to solve, covering the cost of administration and counseling patients about interventions to improve their PROs can be substantial. In liver disease, the best and easiest tool to use is a validated disease-specific instrument (such as the CLDQ), which takes no more than 10 minutes to complete. In fact, these instruments can be completed electronically either during the office visit or before the visit through secure web access. Nevertheless, all of these efforts require strong emphasis and desire to assess the patient's perspective about their disease and its treatment and to manage their quality of life accordingly.

In summary, the armamentarium of PRO tools used in multiple studies of CLD have provided excellent insight into the PRO burden of CLD, and their treatments from the patient's perspective thus are an important part of health care workers' interaction with patients. Work continues in understanding the impact of other liver diseases on PROs but with the current knowledge about PROs, clinicians should be encouraged to use this information when formulating their treatment

Take away points

1. CLD is not only associated with negative clinical outcomes (increased mortality) but also with impairment of patient-reported outcomes (PROs) and economic burden.
2. PROs are surrogates of patient experience and must be included in outcomes assessment to capture the comprehensive burden of disease and its treatment on the patients' lives.
3. Disease-specific PRO instruments such as the chronic liver disease questionnaire (CLDQ, CLDQ-HCV, and CLDQ-NASH) are more responsive to change and more appropriate for clinical trials.

plan.[25] Finally, seamless implementation of PRO assessments in the clinical setting in a cost-effective manner remains a challenge and should be addressed in the future.

References

1. Afendy A, Kallman JB, Stepanova M, et al. Predictors of health-related quality of life in patients with chronic liver disease. Aliment Pharmacol Ther, 2009;30:469-76.

2. Sarin SK, Maiwall R. Global burden of liver disease: a true burden on health sciences and economies. Available from: http://www.worldgastroenterology.org/publications/e-wgn/e-wgn-expert-point-of-view-articles-collection/global-burden-of-liver-disease-a-true-burden-on-health-sciences-and-economies. Accessed: August 31, 2017.

3. Younossi Z, Henry L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology. 2016;150:1778-85.

4. Younossi ZM, Koenig AB,

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Table 1. Tools used to measure patient-reported outcomes in patients with chronic liver disease

Name of tool	Health domains measured	Items, n	Strengths and limitations	Generic or disease-specific	How administered
Short Form 36	Eight domains measuring functional health and well-being, general health, vitality, role emotional, role physical, social well-being, mental health, and physical functioning Two summary scales of physical composite and mental composite scores	36 items	**Strengths:** Most widely used tool worldwide Established population norms for comparison **Limitations:** Generic tool may not be sensitive to disease-specific patient-reported outcome impairments Asks for recall of how patient is feeling over past/week/month, so depends on accurate recall	Generic, general health	Self-administered or can be performed in person or over the telephone Takes 5-10 minutes to complete
Sickness Impact Profile, also the SIP-68	Investigates a change in behavior as a consequence of illness, covers 12 categories of daily living: sleep and rest, eating, work, home management, ambulation, mobility, body care and movement, social integration, alertness behavior, emotional behavior, and communication	136 items/68 items	**Strengths:** Items are scored on numeric scale with higher scores reflecting greater dysfunction Aggregate psychosocial score derived from four categories An aggregate physical score from three categories **Limitations:** The length of time for completion of instrument may result in incomplete surveys It is a generic tool, so it may not be sensitive to disease-specific patient-reported outcome impairments	Generic, general health	Paper and pencil takes approximately 30-40 minutes for the full survey and 15-20 minutes for the SIP-68
Chronic Liver Disease Questionnaire (CLDQ)	Measures four domains: activity and energy, emotional, worry, and systemic, and assesses HRQL in chronic liver disease	29 items using a Likert scale of 1-7, with higher scores meaning a better HRQL	**Strengths:** Widely used and validated tool to measure HRQL in patients with chronic liver disease Translated into many languages (see website: www.cldq.org) **Limitations:** Cannot compare with other chronic diseases	Disease-specific	Paper and pencil or electronic: self-administered takes 10 minutes to complete
Hepatitis C virus–specific CLDQ	Measures four domains: activity and energy, emotional, worry, and systemic, and assesses HRQL in CLD and specifically in patients with HCV	29 items using a Likert scale of 1-7, with higher scores meaning a better HRQL, but questions have been modified to be pertinent to patients with HCV	**Strengths:** Valid and reliable tool that was designed specifically to measure disease-specific HRQL for patients living with chronic hepatitis C **Limitations:** Cannot compare with other chronic diseases	Disease-specific	Paper and pencil or electronic: self-administered takes 10 minutes to complete
CLDQ-NAFLD/NASH	Measures six domains: abdominal symptoms, activity, emotional, fatigue, systemic symptoms, and worry	36 items: 29 items from original CLDQ and 7 new items to reflect a greater influence of fatigue in the NAFLD population	**Strengths:** High correlations between presumably related domains of CLDQ-NAFLD and the widely used and extensively validated Short Form 36 Female patients, older patients, and patients with comorbidities were found to have lower scores in expected domains including physical activity and depression **Limitations:** Further validation needed in patients with NAFLD/NASH cirrhosis, especially decompensated cirrhosis Cannot compare with other chronic diseases	Disease-specific	Paper and pencil or electronic: self-administered takes 10 minutes to complete
Functional Assessment of Chronic Illness Therapy-Fatigue	Developed to measure four primary quality-of- life domains: physical well-being, social/family well-being, emotional well-being, and functional well-being, and the effect of fatigue on these domains	16 questions scored on a 0-4 Likert scale, with higher scores indicating fatigue interference with activity asked about	**Strengths:** Written at fourth-grade reading level Is specifically formatted for ease of self-administration Takes 4-6 minutes to complete Validated for use with special populations such as the elderly and those living in rural areas Appropriate for use in patients with a variety of chronic health conditions, and in the general population **Limitations:** Interviewer training is needed to minimize bias to patient responses	Disease-specific	Patient self-administration, either on paper or direct to computer Face-to-face or phone interview, however, interview administration is appropriate with adequate training of interviewers to minimize bias to patient responses
Fatigue Symptom Severity	Measures the severity of fatigue and its effect on a person's activities and lifestyle in patients with a variety of disorders	Nine-item scale scored on a 7- point scale with 1 = strongly disagree and 7 = strongly agree The minimum score is 9 and the maximum score possible is 63 The higher the score the greater the fatigue severity Another way of scoring: mean of all the scores with the minimum score being 1 and the maximum being 7	**Strengths:** Items formulated as statements about the fatigue experience itself, what causes fatigue, and how fatigue interferes with daily life **Limitations:** Both item changes as well as overall score should be reported when using the scale over time; this is necessary to better understand what area created the change Also, scores from different diagnostic groups cannot be compared across groups, only within groups	Generic that can be modified to be disease-specific	Self-report

Table 1 continued on following page

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Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.

5. Younossi ZM, Park H, Dieterich D, et al. Assessment of cost of innovation versus the value of health gains associated with treatment of chronic hepatitis C in the United States: the quality-adjusted cost of care. Medicine. (Baltimore). 2016;95:e5048.

6. Centers for Disease Control–Health Related Quality of Life. Available from: http://www.cdc.gov/HRQoL/concept.htm. Accessed: August 31, 2017.

7. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res. 2001;10:405-20.

8. De Bruin A, Diederiks J, De Witte L, et al. The development of a short generic version of the Sickness Impact Profile. J Clin Epidemiol. 1994;47:407-12.

9. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trial. 1989;10:407-15.

10. Younossi ZM, Guyatt G, Kiwia M, et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut. 1999;45:295-300.

11. Younossi ZM, Stepanova M, Henry L. Performance and validation of Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV) in clinical trials of patients with chronic hepatitis C. Value Health. 2016;19:544-51.

12. Younossi ZM, Stepanova M, Henry L, et al. A disease-specific quality of life instrument for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: CLDQ-NAFLD. Liver Int. 2017;37:1209-18.

13. Webster K, Odom L, Peterman A, et al. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: validation of version 4 of the core questionnaire. Qual Life Res. 1999;8:604.

14. Golabi P, Sayiner M, Bush H, et al. Patient-reported outcomes and fatigue in patients with chronic hepatitis C infection. Clin Liver Dis. 2017;21:565-78.

15. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4:353-65.

16. Loria A, Escheik C, Gerber NL, et al. Quality of life in cirrhosis. Curr Gastroenterol Rep. 2012;15:301.

17. Younossi ZM, Stepanova M, Charlton M, et al. Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial. Lancet Gastroenterol Hepatol. 2016;1:122-32.

18. Pérez-San-Gregorio MÁ, Martín-Rodríguez A, Domínguez-Cabello E, et al. Quality of life and mental health comparisons among liver transplant recipients and cirrhotic patients with different self-perceptions of health. J Clin Psychol Med Settings. 2013;20:97-106.

19. Younossi ZM, Stepanova M, Henry L, et al. An in-depth analysis of patient-reported outcomes in patients with chronic hepatitis C treated with different anti-viral regimens. Am J Gastroenterol. 2016;111:808-16.

20. Weinstein AA, Price Kallman J, Stepanova M, et al. Depression in patients with nonalcoholic fatty liver disease and chronic viral hepatitis B and C. Psychosomatics. 2011;52:127-32.

21. Younossi ZM, Stepanova M, Jacobson IM, et al. Sofosbuvir and velpatasvir with or without voxilaprevir in direct-acting antiviral-naïve chronic hepatitis C: patient-reported outcomes from POLARIS 2 and 3. Aliment Pharmacol Ther. 2018;47:259-67.

22. Sayiner M, Stepanova M, Pham H, et al. Assessment of health utilities and quality of life in patients with non-alcoholic fatty liver disease. BMJ Open Gastroenterol. 2016;3:e000106.

23. Younossi ZM, Stepanova M, Gordon S, et al. Patient-reported outcomes following treatment of chronic hepatitis C virus infection with Sofosbuvir and Velpatasvir, with or without Voxilaprevir. Clin Gastroenterol Hepatol. 2018;16:567-74.

24. Younossi ZM, Stepanova M, Charlton M, et al. Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial. Lancet Gastroenterol Hepatol. 2016;1:122-32.

25. Younossi Z. What Is the ethical responsibility of a provider when prescribing the new direct-acting antiviral agents to patients with hepatitis C infection? Clin Liver Dis. 2015;6:117-9.

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Table 1. Continued

Name of tool	Health domains measured	Items, n	Strengths and limitations	Generic or disease-specific	How administered
Fatigue Assessment Inventory	Designed to evaluate four domains of fatigue: fatigue severity, situation specificity, consequences of fatigue, and responsiveness to rest/sleep, with extra dimensions providing information on situational aspects of fatigue	29-item scale scored between 1 and 7 by the patient, 1 representing a total disagreement and 7 representing a total agreement with written statements	**Strengths:** Expanded version of the unidimensional Fatigue Symptom Severity (see earlier), with items added to assess additional aspects of fatigue Is able to distinguish healthy subjects from patients and is notable for its ability to distinguish differences between patients with different diagnoses in some cases **Limitations:** Test-retest reliability is only moderate The factor structure indicates that the majority of the items loaded on to the first two factors and only severity and consequences subscales showed concurrent validity based on other measures of fatigue and energy level		Paper and pencil
Work Productivity Activity Impairment-Specific Health Problem	Evaluates impairment in patients' daily activities and work productivity associated with a specific health problem	There are six questions: five for work activity and one for activity of daily living Patients are asked to think about how their disease state impacts their life when answering the questions Work productivity is divided into two parts: presenteeism, how many hours during a work day are patients not productive as a result of their specific disease; and absenteeism, how many days of work are missed as a result of patients' specific disease Higher scores indicate poorer health status and impairment, range is 0-1	**Strengths:** Tool able to capture lost productivity that can be used when determining economic impact of disease states The Work Productivity Activity Impairment has been translated into more than 100 languages through a harmonization process consisting of several independent translations, back translations, expert review of the back translation, and local review by users Free to use **Limitations:** The recall period is 7 days Interviewer administration is associated with better accuracy of responses	Disease-specific	Paper and pencil Have developed a web-based interactive platform

Note: CLDQ-NAFLD/NASH = nonalcoholic fatty liver disease/nonalcoholic steatohepatitis–specific CLDQ; HRQL = health-related quality of life; NASH = nonalcoholic steatohepatitis.

FDA approves pembrolizumab for HCC patients

Especially those treated previously with sorafenib.

BY LUCAS FRANKI

MDedge News

The Food and Drug Administration has approved pembrolizumab immunotherapy injection (Keytruda) for the treatment of patients with hepatocellular carcinoma who were previously treated with sorafenib.

Approval was based on results of KEYNOTE-224, a single-arm, open-label, multicenter trial evaluating pembrolizumab in a group of 104 patients with hepatocellular carcinoma who were either intolerant to or had disease progression with sorafenib, according to a Merck company press release.

The objective response rate was 17%, with a complete response rate of 1% and a partial response rate of 16%. In responding patients, 89% had a response duration of at least 6 months, and 56% had a response duration of at least 12 months.

Adverse events were generally similar to those seen in trials of patients with melanoma or non–small cell lung cancer, and included pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, severe skin reactions, solid organ transplant rejection, and allogeneic hematopoietic stem cell transplantation complications.

"Hepatocellular carcinoma is the most common type of liver cancer in adults, and while we have seen recent therapeutic advancements, there are still limited treatment options for advanced recurrent disease. Today's approval of Keytruda is important, as it provides a new treatment option for patients with hepatocellular carcinoma who have been previously treated with sorafenib," Andrew X. Zhu, MD, lead investigator and director of liver cancer research at Massachusetts General Hospital and professor of medicine at Harvard Medical School, both in Boston, said in the press release.

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References: 1. IQVIA. National Prescription Audit Report. September 2018. **2.** Rex DK, DiPalma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. *Gastrointest Endosc.* 2010;72(2):328-336. **3.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2017. **4.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53.

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