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GI & HEPATOLOGY NEWS

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JEFF CRAVEN/MDEDGE NEWS

Dr. Chandraprakash Umapathy presented risks for readmission of cirrhosis patients at the annual meeting of the American College of Gastroenterology.

LOS, complications predict readmission for cirrhosis patients

BY JEFF CRAVEN
MDedge News

PHILADELPHIA – Patients with cirrhosis have a higher risk of hospital readmission if their length of stay is less than 4 days, if they have cirrhosis-related complications, and if they are discharged to an extended-care facility or to home health care, according to a recent presentation at the annual meeting of the American College of Gastroenterology.

"The presence of cirrhosis-related complications is very strongly associated with readmissions," Chandraprakash Umapathy, MD, MS, from the University of California, San Francisco, Fresno, said during his presentation. "Quality improvement efforts should focus on optimizing the management of complications of cirrhosis in the outpatient setting to reduce readmissions."

See **Cirrhosis** · *page 17*

Key clinical point
11.09% of patients were readmitted at 30 days and 18.74% at 90 days, with the most common reasons for readmission including presence of cirrhosis complications and length of stay less than 4 days.

CMS delays controversial E/M changes in final rule

BY ALICIA GALLEGOS
MDedge News

After a torrent of criticism from the physician community, the Centers for Medicare & Medicaid Services has delayed its proposed collapsing of evaluation and management (E/M) codes into single payments.

The agency's final 2019 Physician Fee Schedule, announced Nov. 1, rescinds a proposal that would have blended payments for new and established patients for office/outpatient E/M levels 2 through 5 into single payments. Instead, the agency will continue to hear perspective on the proposal with plans to collapse E/M code levels 2 through 4 into single payments beginning in 2021, while maintaining level 5.

CMS also pulled back its proposal to apply a multiple procedure payment reduction to E/M visits furnished on the same day as a procedure. Payment rates for the less expensive of the two will be maintained, rather than cut in half as initially proposed.

The final rule released is much different than the one proposed, which shows that CMS heeded concerns by physicians and took time to craft a more realistic fee schedule, said Orly Avitzur, MD, chair of the American Academy of Neurology's Medical Economics and Management Committee. The proposed collapsed E/M levels would have likely led to shorter visit times, negatively im-

See **E/M changes** · *page 4*

Etrasimod improves clinical, endoscopic outcomes in UC patients

BY JEFF CRAVEN
MDedge News

PHILADELPHIA – Use of etrasimod was associated with improved clinical and endoscopic results, and was generally safe and well tolerated compared with placebo in patients with moderate to severe ulcerative colitis, according to a recent award-winning presentation at the annual meeting of the American College of Gastroenterology.

"Patients with moderate to severe ulcerative colitis receiving etrasimod 2 mg per day achieved statis-

See **Etrasimod** · *page 22*

INSIDE

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LETTER FROM THE EDITOR: Stay tuned

Two events that will impact our practices occurred in November: 1) an election and 2) the Centers for Medicare & Medicaid Services final rule. The election returned us to a split government with Democrats controlling the U.S. House and Republicans controlling the Senate (without a filibuster-proof majority). This means that ACA repeal and dramatic alterations to Medicaid will be off the table. Pressures on ACA's margins will remain in both the legislative and judicial arms of government. Federal and state governments will continue to try to stabilize the individual markets by using reinsurance and premium support. The number of states expanding Medicaid eligibility will continue to grow (now at 37). There will be further pressure on drug pricing, likely targeted to Part B and 340b drugs. This will affect academic centers and hospital margins substantially.

DR. ALLEN

CMS issued it final rule for the Physician Fee Schedule. AGA and the other GI societies have published a detailed member alert that can be found here: http://ow.ly/I6Xg30mDRVd. Key points involve simplified documentation for evaluation and management visits, site-neutrality reimbursement for clinic visits, identification of colonoscopy and EGD codes for CMS review, and changes in calculating practice expense, among others. MACRA rules are evolving with further pressure on practices and health systems to evolve into alternative payment models. Commercial insurers are finally near a tipping point in pressing for two-sided risk contracts. Practices should be alert for local and regional pressures around price transparency and narrow networks. Health systems (including academic centers) must plan for margin reductions due to changes in pharmacy reimbursement, network price tiering, a continued shift toward government payers, and other pressures that could drive large systems into the red.

For the first time since 1996, discretionary programs including NIH, CDC, AHRQ, and VA research all have been included in a budget (as opposed to a Continuing Resolution) that was passed by Congress and signed into law. This gives us some stability and predictability; however, the looming (and increasing) budget deficit will prompt Congress to increase fiscal pressure on domestic programs such as Social Security, Medicare, and Medicaid. Stay tuned and stay involved.

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

DDSEP eight Quick Quiz

Q1. A 45-year-old woman presents with a 3-year history of a sense of incomplete evacuation, excessive straining to defecate, and rectal bleeding. Colonoscopy demonstrates an irregular, polypoid lesion on the anterior wall of the rectum. Biopsies reveal fibromuscular obliteration of the lamina propria and hypertrophied muscularis mucosa with extension of muscle fibers upward between the crypts.

Which of the following diagnostic tests are indicated for further evaluation of this condition?
A. Defecography
B. Rectal suction biopsies
C. Colonic transit testing
D. MR enterography
E. IBD serologies

Q2. A 26-year-old woman presents for an evaluation of an 8-month history of intermittent abdominal pain, which is associated with diarrhea. Her pain improves with bowel movements. She denies weight loss, GI bleeding, or nocturnal symptoms. There is no family history of IBD or celiac disease. Physical examination is normal. Thyroid function testing, C-reactive protein, celiac serology, stool studies for infectious pathogens, stool calprotectin, and colonoscopy with biopsies are all negative.

Which of the following is NOT currently indicated for the management of this patient's condition?
A. Alosetron
B. Antispasmodics
C. Rifaximin
D. Probiotics
E. Tricyclic antidepressants (TCAs)

The answers are on page 18.

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The AGA Institute headquarters is located at 4930 Del Ray Avenue, Bethesda, MD 20814, ginews@gastro.org.
Editorial Offices 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548
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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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CMS heard physicians

E/M changes *from page 1*

pacting the doctor-patient relationship and patient care, she said.

As part of its final rule, CMS moved forward with several other changes to coding and documentation, including eliminating the need to document the medical necessity of a home visit in lieu of an office visit, and allowing physicians to skip documentation of changes since a prior patient visit when relevant information is already contained in the record.

Additionally, the final rule clarifies that for E/M office/outpatient visits physicians do not need to re-enter information on the patient's chief complaint and history that has already been entered by ancillary staff or the patient. The physician may just indicate in the medical record that he or she has reviewed and verified the information.

In a statement, CMS administrator Seema Verma said the final rule cements dramatic improvements for clinicians and patients and reflects extensive input from the medical community.

"Addressing clinician burnout is critical to keeping doctors in the workforce to meet the growing needs of America's seniors," Ms. Verma said in the statement. "[The] rule offers immediate relief from onerous requirements that contribute to burnout in the medical profession and detract from patient care. It also delays even more significant changes to give clinicians the time they need for implementation and provides time for us to continue to work with the medical community on this effort."

"In the final rule, CMS acknowledges concerns from physicians regarding many aspects of the proposed

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rule," said Anton Decker, MD, chair of the American Gastroenterological Association's Practice Management and Economics Committee. "In particular, proposed revisions to E/M services would have negatively impacted the doctor-patient relationship and patient care, especially for the most complex patients," he said.

"Overall, the AGA is pleased that CMS listened to concerns and reversed certain proposals such as the multiple procedure payment reduction for E/M visits furnished on the same day as a procedure," Dr. Decker said. "We are also pleased that CMS is giving stakeholders an additional 2 years to provide input on how best to refine E/M documentation and coding."

Shivan Mehta, MD, MBA, AGA's adviser to the American Medical Association Relative-Value Update Committee (RUC), the body that provides code value recommendations to CMS, noted, "Although CMS heeded concerns from physicians

Continued on following page

AGA GUIDELINE

Treatment of opioid-induced constipation

BY AMY KARON
MDedge News

For patients with suspected opioid-induced constipation, start by taking a careful history of defecation and dietary patterns, stool consistency, incomplete evacuation, and "alarm symptoms," such as bloody stools or weight loss, states a new guideline from the American Gastroenterological Association in the journal Gastroenterology.

Clinicians also should rule out other causes of constipation, such as pelvic outlet dysfunction, mechanical obstruction, metabolic abnormalities, and comorbidities or concurrent medications, wrote Seth D. Crockett, MD, MPH, of the University of North Carolina at Chapel Hill, together with his associates.

Opioid therapy can lead to a range of gastrointestinal symptoms, such as constipation, gastroesophageal reflux, nausea and vomiting, bloating, and abdominal pain. Among these, constipation is by far the most common and debilitating, the guideline notes. In past studies, 40%-80% of patients who received opioids developed opioid-induced constipation (OIC), a more severe presentation that involves a combination of reduced stool frequency in addition to other symptoms, such as harder stools, new or worsening straining during defecation, and a sense of incomplete rectal evacuation.

Treating OIC should start with lifestyle interventions, such as drinking more fluids, toileting as soon as possible when feeling the urge to defecate, and adding regular moderate exercise whenever tolerable, the guideline advises. For patients on oral or parenteral therapy, consider switching to an equianalgesic dose of a less-constipating opioid, such as transdermal fentanyl or oxycodone-naloxone combination therapy.

Many patients with OIC require interventions beyond lifestyle changes or opioid switching. For these patients, the guideline advises starting with conventional laxative therapies based on their safety, low cost, and "established efficacy" in the OIC setting. Options include stool softeners (docusate sodium), osmotic laxatives (polyethylene glycol, magnesium hydroxide, magnesium citrate, and lactulose), lubricants (mineral oil), and stimulant laxatives (bisacodyl, sodium picosulfate, and senna). "Of note, there is little evidence that routine use of stimulant laxatives is harmful to the colon, despite widespread concern to the contrary," the guideline states. Although randomized, controlled trials have not evaluated particular laxative combinations or titrations for OIC, the best evidence supports stimulant and osmotic laxative therapy, the authors note.

Before deeming any case of OIC laxative refractory, ensure that a patient receives an adequate trial of at least two classes of laxatives administered on a regular schedule, not just "as needed," the guideline specifies. For example, a patient might receive a 2-week trial of a daily osmotic laxative plus a stimulant laxative two to three times weekly. The guideline authors suggest restricting the use of enemas to rescue therapy. They also note that consuming more fiber tends not to help patients with OIC because fiber does not affect colonic motility.

For truly laxative-refractory OIC, the guidelines recommend escalating treatment to peripherally acting mu-opioid receptor antagonists (PAMORAs). These drugs restore the function of the enteric nervous system by blocking mu-opioid receptors in the gut. Among the PAMORAs, the guideline strongly recommends the use of naldemedine or naloxegol over no treatment, based on robust data from randomized, double-blind, placebo-controlled trials. In the phase 3 COMPOSE 1, 2, and 3 trials, about 52% of patients who received naldemedine achieved at least three spontaneous bowel movements per week, compared with 35% of patients who received placebo. Additionally, in a 52-week safety and efficacy study (COMPOSE 3), naldemedine was associated with one more spontaneous bowel movement per week versus placebo and with a low absolute increase in adverse events.

The guideline bases its strong recommendation for naloxegol on moderate-quality data from three studies, including two phase 3, double-blind, randomized, placebo-controlled trials. Although at least five randomized, controlled trials have evaluated methylnaltrexone, the evidence was low quality, and therefore the guideline only conditionally recommends prescribing this PAMORA over no treatment.

The guideline also makes no recommendation on the use of the intestinal secretagogue lubiprostone or the 5HT agonist prucalopride. Studies of lubiprostone were limited by possible reporting bias and showed no clear treatment benefit, the authors state. They describe a similar evidence gap for prucalopride, noting that at least one trial ended early without publication of the findings. They recommend further studying lubiprostone as well as prucalopride and other highly selective 5-HT4 agonists for treating OIC. Head-to-head trials would help guide treatment choice for patients with laxative-refractory OIC, they add. "Cost-effectiveness studies are also lacking in this field, which could inform prescribing strategy, particularly for newer, more expensive agents."

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SOURCE: Crockett SD et al. Gastro. 2019. doi: 10.1053/j.gastro.2018.07.016.

Continued from previous page

on many aspects on the proposed rule, in a surprise move, CMS took direction from Anthem Inc., a large health insurance company, and recommended two endoscopy services be revalued by the AMA's RUC. Private health insurers don't typically influence the appropriateness of Medicare payment amounts, and we question Anthem's motivation as commercial payers frequently link their payment rates to a percentage of Medicare payment amounts or use those amounts as benchmarks when negotiating physician contracts."

CMS finalized a number of proposals to pay doctors separately for communication technology services. This includes HCPCS code G2012 for brief communication technology-based services, such as virtual check-ins and HCPCS code G2010 for remote evaluation of a recorded video and/or images submitted by an established patient, also known as store and forward.

'In a surprise move, CMS took direction from Anthem Inc., a large health insurance company, and recommended two endoscopy services be revalued by the AMA's RUC. Private health insurers don't typically influence the appropriateness of Medicare payment amounts, and we question Anthem's motivation.'

Additionally, CMS will pay separately for new codes that describe chronic care remote physiologic monitoring (CPT codes 99453, 99454, and 99457) and interprofessional Internet consultation (CPT codes 99451, 99452, 99446, 99447, 99448, and 99449). Also new to the list of reimbursable telehealth services are HCPCS codes G0513 and G0514 for prolonged preventive services.

Telehealth physicians who treat opioid use disorder received more flexibility under the CMS 2019 fee schedule through the agency's removal of originating site geographic requirements. CMS will now allow a patient's home to be an originating site for telehealth services for substance use disorder treatment or co-occurring mental health disorder. The agency is also accepting comments on a new Medicare benefit category for opioid use disorder treatment furnished by opioid treatment programs under Part B beginning on or after Jan. 1, 2020.

CMS also approved updates to its Medicare Shared Savings Program, including finalizing time-sensitive program policy changes for currently participating Accountable Care Organizations (ACOs). These changes include the following:

- Having a voluntary 6-month extension for existing ACOs whose participation agreements expire on Dec. 31, 2018, and the methodology for determining financial and quality performance for the 6-month performance year from Jan. 1 to June 30, 2019.
- Revising the definition of primary care services used in beneficiary assignment.
- Providing relief for ACOs and their clinicians impacted by extreme and uncontrollable circumstances in 2018 and subsequent years.

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Midterm election boosts Medicaid expansion, but challenges remain

BY PHIL GALEWITZ,
KAISER HEALTH NEWS

Medicaid – which has been a political football between Washington and state capitols during the past decade – scored big in the Nov. 6 election.

Following the vote, nearly 500,000 uninsured adults in five states are poised to gain Medicaid coverage under the Affordable Care Act, advocates estimate. Three deep-red states passed ballot measures expanding their programs and two other states elected governors who have said they will accept expansion bills from their legislatures.

Medicaid proponents also were celebrating the Democrats' takeover of the House, which would impede

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any Republican efforts to repeal the ACA and make major cuts to the federal-state health insurance program for low-income people.

"Tuesday was huge for the Medicaid program," said Katherine Howitt, associate director of policy at Community Catalyst, a Boston-based advocacy group. "The overall message is that the electorate does not see this as a Democrat or GOP issue but as an issue of basic fairness, access to care, and pocketbook issue. Medicaid is working and is something Americans want to protect."

David K. Jones, PhD, of the department of health law, policy and management at Boston University School of Public Health said ballot organizers now have a blueprint on how to expand Medicaid in states that have resisted. "I see this as a turning point in ACA politics," he said. Still, he added, "it's not inevitable."

Medicaid is the largest government health program, insuring at least 73 million low-income Americans. Half of them are children. To date, 32 states and the District of Columbia have expanded it under the ACA. Before that law, Medicaid was generally limited to children, sometimes their parents, pregnant women, and people with disabilities.

The ACA encouraged states to open the program to all Americans earning up to 138% of the poverty level ($16,753 for an individual in 2018). The federal government is paying the bulk of the cost: 94% this year, but gradually dropping to 90% in 2020. States pay the rest.

GOP opposition has left about 4.2 million low-income Americans without coverage in various states.

"It's not over until it's over is the story of Medicaid expansion and the Affordable Care Act as the politics never ends and the opportunity for obstruction never ends," said Dr. Jones. "But the trend overall has been to increasing implementation and increasing coverage."

Montana fails to endorse funding

Two years after President Trump carried Idaho, Nebraska, and Utah by double-digit margins with a message that included repeal of the ACA, voters in those states approved the ballot referendums on Nov. 6. Together, the states have about 300,000 uninsured adults who would be eligible for the program.

In addition, Democrats secured the governor's offices in Kansas and Maine, which will increase the likelihood those states will pursue expansion. Legislatures in both states have previously voted to expand, only to have GOP governors block the bills. Maine voters also passed a referendum in 2017 endorsing expansion, but Republican Gov. Paul LePage again refused to accept it.

Current and incoming Republican governors in Idaho and Utah said they wouldn't block implementation of the effort if voters approved it. Nebraska Gov. Pete Ricketts (R) said on Nov. 7 he would follow the will of the voters but would not support paying for it with a tax increase.

It wasn't a clean sweep, however, for Medicaid.

In preliminary results, a ballot issue to fund Montana's Medicaid expansion – which is already in place and slated to expire next July – was failing. Tobacco companies had mounted a campaign to stop the measure, which would have partially financed the expansion with taxes on tobacco products.

The Montana legislature and the Democratic governor are expected to address the issue in the session that starts in January. No state has reversed its Medicaid expansion, even though GOP governors in Kansas and Arkansas have threatened to do so.

Nearly 100,000 Montana residents have received Medicaid since its expansion, twice as many as expected.

Nancy Ballance, the Republican chairwoman of the Montana House Appropriations Committee who opposed the bill that expanded Medicaid in 2015, said she is confident the state legislature will extend the program past July. But she expects the legislature to put some limits on the program, such as adding an asset test and work requirements.

"There are some people in the state who may not have disabilities but need some help to access coverage," she said. "I think we can pass something without people having a gap in coverage. … That will be a priority."

"It was never our intent to simply sunset the expansion and have it go away," she said. Rather, the legislature put the sunset provision in to revisit the provision to make any changes.

Chris Jacobs, a conservative health policy analyst in Washington, said the Montana results showed that when voters are given a choice of having to pay for Medicaid expansion through a new tax, they were not willing to go along.

But in Utah, voters did agree to fund their state plan by adding 0.15% to the state's sales tax, just over a penny for a $10 purchase.

Fernando Wilson, acting director of the Center for Health Policy at the University of Nebraska Medical Center in Omaha, said the vote on the state's ballot question indicated many people wanted to help 80,000 uninsured Nebraskans gain coverage.

"I think it showed there was a clear need for it," he said. The legislature likely won't block the expansion, Mr. Wilson said, though it may try to add a conservative twist such as adding premiums or other steps.

Sheila Burke, a lecturer in health policy at Harvard Kennedy School in Cambridge, Mass., said voters approved Medicaid expansion not just because it would help improve health coverage for their residents but to help stabilize their hospitals, particularly those in rural areas. Hospitals have said this step helps their bottom lines because it cuts down on uninsured patients and uncompensated care.

"The broad population does see the value of Medicaid," she said. "They saw it as a loss by their states not to accept the federal funds," she said.

Despite the victories, Ms. Burke said, advocates should not assume other states such as Florida, Tennessee, and Texas will follow suit.

"I don't see a radical shift, but it moves us closer," she said.

'Fertile ground' for more referenda

If advocates press for more referenda, Florida might be a tempting target. More than 700,000 adults there could become eligible, but the campaign would likely also be very costly.

Jonathan Schleifer, executive director of the Fairness Project, which financed the ballot initiatives in Maine in 2017 and the four states this year, refused to say which states would be targeted next.

The group is funded by the Service Employees International Union–United Healthcare Workers West, a California health care workers union.

"The GOP has been bashing the ACA for nearly a decade, and voters in the reddest states in the country just rejected that message," Mr. Schleifer said. "It's a repudiation and a tectonic shift in health care in this country."

"There is fertile ground" for more such ballot votes, said Topher Spiro, vice president for health policy at the Center for American Progress, a liberal think tank. "It is clear that public opinion is on the side of Medicaid expansion and the election results merely confirm that."

The election results also could have consequences on efforts by states to implement work requirements for Medicaid enrollees.

Michigan and New Hampshire – which expanded the program but recently won federal approval to add controversial work requirements – could revisit that additional mandate as a result of Democrats winning control over the governor's office in Michigan and both houses of the legislature in New Hampshire.

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FROM THE AGA JOURNALS

Surgical model describes reflux esophagitis after esophagojejunostomy

BY CALEB RANS
MDedge News

During a wound repair process in rats, metaplastic columnar-lined esophagus was produced and increased in length following esophagojejunostomy, which may be independent of stem cell reprogramming, according to results from an anastomosed rodent study.

The investigators studied esophageal and tissue sections of 52 rats at different time points after esophagojejunostomy, and samples were analyzed for length, type, and location of columnar lining. In addition, the sections were examined immunophenotypically to elucidate the molecular changes that occur during ulceration. Agoston T. Agoston, MD, PhD, of Brigham and Women's Hospital and the department of pathology at Harvard Medical School, Boston, and colleagues reported the findings in Cellular and Molecular Gastroenterology and Hepatology.

"This rodent columnar-lined esophagus has been proposed to develop from cellular reprogramming of progenitor cells, but studies on early columnar-lined esophagus development are lacking," the researchers wrote.

In the model, ulceration was seen 2 weeks after surgery, which began distally at the esophagojejunal anastomosis. Representative of wound healing, reepithelialization of the ulcer region took place through formation of immature glands, which were found to bud directly from jejunal crypts.

Key clinical point
In an esophageal tissue section, columnar-lined esophagus length was elongated from 0.15 (±0.1) mm to 5.22 (±0.37) mm at 2 and 32 weeks, respectively, after esophagojejunostomy.

After immunophenotypic analysis, the researchers reported that "immunohistochemical characterization of neoglandular epithelium located immediately proximal to the anastomosis showed features similar to those of the native nonproliferating jejunal epithelium located immediately distal to the anastomosis." They further reported that "the columnar-lined esophagus's immunoprofile was similar to jejunal crypt epithelium."

Upon further examination of the ulcer segment, Dr. Agoston and colleagues found that columnar-lined esophagus elongated from 0.15 mm (standard error of the mean, ± 0.1) to 5.22 mm (SEM, ± 0.37) at 2 and 32 weeks post esophagojejunostomy, respectively.

"There was a highly significant linear relationship between the length of the neoglandular epithelium in the distal esophagus and the number of weeks after surgery (correlation coefficient, 0.94; *P* less than .0001)," the investigators stated.

Locational analysis revealed epithelial-mesenchymal transition markers being expressed by spindle-shaped cells at the leading edge of the columnar-lined esophagus. In addition, neoglands were identified within esophageal ulcer beds and actively dividing squamous epithelium was seen exclusively at the proximal ulcer border.

Following the systematic analysis, the authors noted that the columnar-lined esophagus was most likely the result of jejunal cell migration into the esophagus. They suggested that if compared jejunal cells may competitively dominate squamous cells in the context of chronic gastroesophageal reflux disease. Furthermore, they observed that the region of ulceration following esophagojejunostomy in their model was more expansive than that reported in other comparable rodent models of reflux esophagitis.

'Using a rat model of reflux esophagitis via surgical esophagojejunostomy, we have shown that a metaplastic, columnar-lined esophagus develops via a wound healing process, and not via genetic reprogramming of progenitor cells.'

"The reason for this difference is not clear, but we speculate that it is the result of technical aspects of our reflux-inducing surgery," the researchers wrote. They further explained that "we intentionally fashioned a large anastomotic orifice between the esophagus and jejunum, perhaps larger than that fashioned by other investigators." And they concluded, "we suspect that this larger orifice resulted in esophageal exposure to larger volumes of refluxate and, consequently, larger areas of ulceration."

The authors acknowledged their results may not be fully applicable in the context of human Barrett's esophagus, given the rodent model. However, they do believe the findings may provide a basis to help understand the wound repair process, particularly the distal edge of ulcers that border the columnar epithelium.

"Using a rat model of reflux esophagitis via surgical esophagojejunostomy, we have shown that a metaplastic, columnar-lined esophagus develops via a wound healing process, and not via genetic reprogramming of progenitor cells," the researchers concluded.

The study was supported by grant funding from the National Institutes of Health and the Baylor Scott and White Research Institute. The authors reported no conflicts of interest.

ginews@gastro.org

SOURCE: Agoston AT et al. Cell Mol Gastroenterol Hepatol. 2018 Jun 26. doi: 10.1016/j.jcmgh.2018.06.007.

Agoston et al. reported that metaplastic columnar-lined esophagus develops in a wound healing process on the distal edge of the ulcer, starting distally at the esophagojejunal anastomosis in the esophagojejunal anastomosed rat model. They also concluded that the columnar-lined esophagus was caused through migration of jejunal cells into the esophagus.

These new findings bring up a couple of issues. One is that metaplastic columnar-lined esophagus originates from jejunal crypt budding over the anastomosis. Some researchers may think this is not metaplasia, as there is no reprogramming of the stem cells. However, the definition of metaplasia is an endpoint such that a normal lineage is placed in an abnormal position, and it can be called metaplasia even it is from budding of jejunal crypt. This new finding is not denying metaplasia.

The second issue is whether these rodent models are really mimicking human metaplastic columnar-lined esophagus or not. In humans, metaplastic columnar-lined esophagus usually accompanies gastroesophageal reflux, but jejunum is not next to esophagus, and jejunal crypt budding is less likely. However, it is common to observe ulcerated lesions in the proximal front of long-segment Barrett's esophagus in humans. In this process, the model of Agoston et al. is describing the human metaplastic columnar-lined esophagus elongation.


DR. NOMURA

There would be more reprogramming happening in the body of animals under the effect of microenvironment. This is a kind of adaptation, and analyzing key factors for this reprogramming would be the path to clarifying carcinogenesis in the metaplastic field and also a way to advance regenerative medicine.

Sachiyo Nomura, MD, PhD, AGAF, FACS, is an investigator in gastrointestinal carcinogenesis and epithelial biology, and a gastrointestinal surgeon, at University of Tokyo Hospital, department of stomach and esophageal surgery, as well as an associate professor, department of gastrointestinal surgery, graduate school of medicine, at the university. She has no conflicts.

FROM THE AGA JOURNALS

Maintaining virologic response predicted long-term survival in HBV patients with decompensated cirrhosis

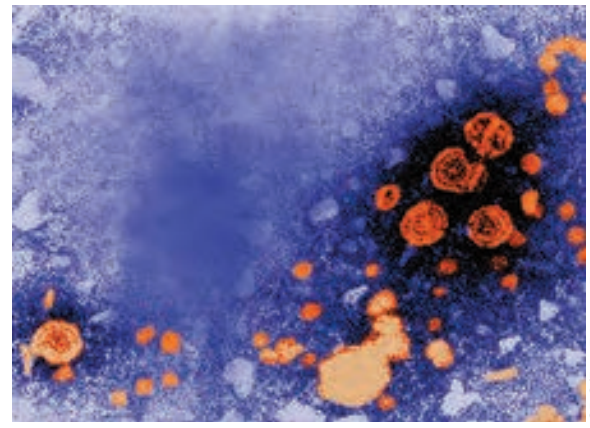
BY AMY KARON
MDedge News

Patients with chronic hepatitis B virus infection and decompensated cirrhosis who immediately initiated entecavir or lamivudine therapy and maintained a virologic response had significantly longer transplant-free survival than did nonresponders, according to the results of a multicenter observational study published in the December issue of Clinical Gastroenterology and Hepatology.

Survival times were "excellent" if patients survived the first 6 months of antiviral therapy and did not develop hepatocellular carcinoma, said Jeong Won Jang, MD, of the Catholic University of Korea College of Medicine in Seoul, South Korea, and his associates. Patients who developed hepatocellular carcinoma had persistent declines in survival over time, they said. Predictors of short-term mortality included a baseline Model for End-Stage Liver Disease score above 20 and multiple complications.

Chronic hepatitis B virus (HBV) infection is the most common cause of liver-related disease and death in Asia, and complications such as decompensated cirrhosis affect up to 40% of chronically infected persons. Five-year survival rates are as low as 14% if patients develop decompensated cirrhosis.

To explore whether virologic suppression with oral nucleoside or nucleotide analog therapy improves outcomes in these decompensated patients, the researchers studied 295 such individuals from the Epidemiology and Natural History of Liver Cirrhosis in Korea Study. At baseline, these patients did not have



CDC/Dr. Erskine Palmer

documented chronic hepatitis C virus infection, hepatocellular carcinoma, other cancers, autoimmune hepatitis, or alcohol use disorders. All patients initiated entecavir or lamivudine therapy immediately after their cirrhosis became decompensated. The primary outcome was transplant-free survival.

A total of 60.1% of patients survived 5 years and 45.7% survived 10 years without undergoing transplantation, for a median transplant-free survival time of 7.7 years. The 116 patients (39%) who consistently had undetectable HBV DNA levels (less than 20 IU/mL) throughout treatment had significantly longer transplant-free survival than did patients who did not maintain a virologic response (*P* less than .001). In addition, a maintained virologic response (MVR) was the strongest predictor of long-term transplant-free survival, the researchers said.

A significantly greater proportion of patients who received entecavir survived 10 years compared with patients who received lamivudine. However, there was no significant difference in long-term survival among patients with MVRs to either drug. "Importantly, it appears that improvement in patient survival is attained by antiviral response, not by the type of nucleos(t)ide analogue per se," the researchers wrote.

Patients who achieved MVR also showed significant improvements in hepatic function, but "the preventive effects of MVR on the incidence of hepatocellular carcinoma appeared only modest," the investigators said. "Survival of patients without hepatocellular carcinoma who survived the first 6 months after initiation of antiviral therapy was excellent, with only a 25.3% mortality rate occurring between 6 months and 10 years."

Based on their findings, Dr. Jang and his associates recommended aiming for an HBV DNA load less than 20 IU/mL in patients with decompensated cirrhosis to significantly improve the chances of long-term survival. Survival curves were similar regardless of whether patients had HBV DNA levels less than 10 IU/mL or between and 10 and 20 IU/mL, they noted.

Funders included Korea Healthcare Technology R&D Project and the Catholic Research Coordinating Center of the Korea Health 21 R&D Project, both of the Ministry of Health and Welfare, Republic of Korea. Dr. Jang disclosed ties to Bristol-Myers Squibb, Gilead, and Merck Sharp & Dohme. Three coinvestigators also disclosed ties to Gilead, MSD, and several other pharmaceutical companies.

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SOURCE: Jang JW et al. Clin Gastroenterol Hepatol. 2018 May 18. doi: 10.1016/j.cgh.2018.04.063.

Norfloxacin might benefit patients with advanced cirrhosis and low ascites fluid protein levels

BY AMY KARON
MDedge News

Six months of once-daily norfloxacin therapy did not reduce 6-month mortality among patients with Child-Pugh class C cirrhosis who had not recently received fluoroquinolone therapy.

Mortality based on the Kaplan-Meier method was 14.8% in the norfloxacin group versus 19.7% for patients receiving placebo (*P* = .21). "Norfloxacin, however, appear[ed] to increase survival of patients with low ascites fluid protein concentrations," wrote Richard Moreau, MD, of Hôpital Beaujon, Paris, and his associates. The results of the multicenter, double-blind trial of 291 patients were published in the December issue of Gastroenterology.

Patients with advanced cirrhosis often develop spontaneous bacterial peritonitis and other severe bacterial infections, with potentially grave outcomes. These are often enteric gram-negative bacteria that cross the intestinal barrier, enter the systemic circulation, and travel to the site of infection.

Long-term fluoroquinolone therapy (typically with norfloxacin) might help prevent these bacterial infections, the translocation of bacterial products, systemic inflammation, and consequent end-organ dysfunction, such as acute kidney disease. However, long-term antibiotic therapy also raises the specter of multidrug resistance, which is especially concerning when it involves a crucial antibiotic class such as fluoroquinolones, the researchers noted. "[In] patients receiving prolonged fluoroquinolone therapy, the development of infections by multidrug resistant bacteria might obscure the beneficial effect of fluoroquinolones on survival," they added.

Four previous blinded and placebo-controlled trials have investigated fluoroquinolone therapy and mortality patients with cirrhosis, but they were small, usually included mortality only as a secondary outcome, and yielded mixed results. Hence, the researchers enrolled 291 patients with advanced (Child-Pugh class C) cirrhosis from 18 clinical sites in France and randomly assigned them to receive either norfloxacin (400 mg once daily) or placebo for 6 months. Patients were evaluated monthly during treatment and then at 9 months and 12 months. The primary outcome was survival at 6 months.

In a post hoc analysis, the researchers examined cumulative

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GI & HEPATOLOGY NEWS

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Prolonged antimicrobial use in patients with decompensated cirrhosis is an area of unclear mortality benefit and may actually increase risk in some patients given antimicrobial resistance. This randomized double-blind, placebo-controlled trial by Moreau et al. evaluates the mortality associated with long-term fluoroquinolone therapy in patients without indications for primary or secondary prophylaxis. Although the study had limited statistical power to detect clear benefit, the authors found that 6-month mortality was not reduced in patients with Child-Pugh class C cirrhosis who received treatment with daily oral fluoroquinolone therapy for 6 months. Subgroup analysis of individuals with ascites fluid total protein levels lower than 15 g/L showed a survival benefit at 6 months.

DR. WATTACHERIL

Determining quantifiable risk for known factors associated with liver disease mortality is a pressing issue, especially in the pretransplant setting where infectious risk is compounded post transplant with changes in gut flora, addition of potent immunosuppressants, and increased metabolic demands.

Studying patients with advanced and decompensated liver disease in a systematic, longitudinal manner with any pharmacologic intervention is a challenge given the unpredictable nature of decompensation events. However, attempts to quantify risk and benefit even in this unpredictable patient population is worthwhile to stratify patients for interventions and minimize risk of liver-related and overall mortality – as well as peritransplant complications and posttransplant survival.

Julia J. Wattacheril, MD, MPH, is a physician-scientist and director of the Nonalcoholic Fatty Liver Disease Program in the Center for Liver Disease and Transplantation at Columbia University Irving Medical Center – New York Presbyterian Hospital; an assistant professor, department of medicine, division of digestive and liver diseases at the Columbia University Vagelos College of Physicians and Surgeons. She has no conflicts.

FROM THE AGA JOURNALS

Thiopurines linked to zoster in IBD patients

BY AMY KARON
MDedge News

For patients with inflammatory bowel disease (IBD), thiopurine exposure was associated with a significantly increased risk of herpes zoster, compared with 5-aminosalicylic acid (5-ASA) monotherapy, according to the results of two large retrospective cohort studies published in the December issue of Clinical Gastroenterology and Hepatology.

In the multivariable analysis, thiopurine monotherapy was linked to about a 47% increase in the risk of herpes zoster, compared with 5-ASA monotherapy (adjusted hazard ratio, 1.47; 95% confidence interval, 1.31-1.65; *P* less than .001). Combination therapy with thiopurines and tumor necrosis factor (TNF) antagonists conferred about a 65% increase in zoster risk (aHR, 1.65; 95% CI, 1.22-2.23; *P* = .001). However, TNF–antagonist monotherapy did not appear to significantly increase the risk of zoster when compared with 5-ASA monotherapy, reported Nabeel Khan, MD, of the University of Pennsylvania in Philadelphia, and his associates.

"Compared to [patients without] IBD, ulcerative colitis (UC) and Crohn's disease (CD) each were associated with significantly increased risk of herpes zoster infection," the researchers wrote online in Clinical Gastroenterology and Hepatology. "With the approval of a new and potentially safer vaccine for herpes zoster, the effects of immunization of patients with IBD should be investigated."

Past studies have linked IBD with a 1.2- to 1.8-fold increase in the risk of zoster, but these studies date to the prebiologic era or excluded patients who were in their mid 60s or older, the researchers wrote. "Additionally, these prior studies have not assessed the validity of the codes used to identify herpes zoster and also did not account for the impact of vaccination," they added. "They also did not take into consideration the severity of the disease or degree of steroid exposure."

Therefore, the researchers conducted two retrospective cohort studies of patients in the United States Veterans Administration between 2000 and 2016. The first cohort study compared the incidence of herpes zoster among patients with IBD who received 5-ASA alone with matched patients without IBD. The second cohort study measured the incidence of herpes zoster in patients with IBD who received various medications and combination regimen. "The VA has a predominantly older population, which makes it an ideal cohort to study herpes zoster incidence in a high-risk population," the investigators noted. "Unlike insurance databases, the VA database can be validated internally and vaccination records are documented."

After adjustment for age, race, sex, geographic region, disease flare, corticosteroid use, and baseline comorbidities, the estimated hazard of developing herpes zoster was 1.81 (95% confidence interval, 1.56-2.11) among patients with ulcerative colitis and 1.56 (95% CI, 1.28-1.91) among patients with Crohn's disease, as compared with patients without IBD. Regardless of their age or the medications they were receiving, patients with IBD had a higher incidence of zoster than the oldest group of patients without IBD (older than 60 years), regardless of age or medication. "The highest risk of herpes zoster was observed in patients with IBD who were less than 60 years of age and on combination therapy," the investigators wrote. "Patients with IBD younger than 50 years who were on combination therapy had higher risk of herpes zoster, compared with patients with IBD older than 60 years of age who were not on immunosuppressive therapy." Based on the findings, they recommended studying the efficacy of widespread use of the new herpes zoster vaccine in patients with IBD.

Pfizer provided unrestricted research funding but was not otherwise involved in the study. One coinvestigator disclosed ties to Pfizer and several other pharmaceutical companies. The remaining investigators reported having no conflicts of interest.

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SOURCE: Khan N et al. Clin Gastroenterol Hepatol. 2018 Jan 5. doi: 10.1016/j.cgh.2017.12.052.

Patients with inflammatory bowel disease are thought to have altered immune regulation, which may increase the risk of systemic complications including infections like herpes zoster. Many of the prior studies assessing the risk of herpes zoster in IBD patients were done before the advent of biologics and excluded older patients, thereby limiting their utility.

This study by Khan et al. aimed to better estimate the incidence and risk factors for development of herpes zoster and to determine the effect of immunosuppressant use on this risk. In two large, retrospective cohort studies they found that, compared with patients without IBD, patients with IBD had a significantly increased risk of developing herpes zoster. Furthermore, this risk was higher in those with recent or cumulative steroid use and in those treated with thiopurines (as monotherapy or in combination with anti-TNF agents). Interestingly, exposure to TNF antagonists alone was not associated with an increased risk of herpes zoster infection.


DR. SHUKLA

This study helps to better clarify the risk of important infections such as herpes zoster in patients with IBD; perhaps more importantly, it informs readers that the risk is increased even in those not on immunosuppressants. These findings should urge practitioners to pay close attention to health maintenance recommendations when caring for IBD patients, specifically appropriate immunizations. With the advent of an inactivated vaccine option against zoster, the benefits of vaccinating patients may be invaluable while risks are minimal and widespread vaccination should be considered.

Richa Shukla, MD, assistant professor, section of gastroenterology and hepatology, Baylor College of Medicine, Houston. She reported no conflicts.

Continued from page 10

death rates at 6 months after accounting for liver transplantation as a competing risk of death and including survival data for patients who developed spontaneous bacterial peritonitis. With this approach, the estimated cumulative rate of death at 6 months was 15.5% (95% confidence interval, 10.1-21.9) in the norfloxacin group and 24.8% (95% CI, 18.1-32.1) in the placebo group, for a hazard ratio of 0.59 (95% CI, 0.35-0.99). Among patients whose ascites fluid levels were less than 15 g/L, the hazard ratio for death at 6 months was 65% lower in the norfloxacin group than in the placebo group (HR, 0.35; 95% CI, 0.13-0.93). Norfloxacin showed no such benefit for patients with ascites fluid levels above 15 g/L.

Norfloxacin therapy "could reduce the incidence of death among patients with ascitic fluid protein concentrations of less than 15 g/L but not among those with ascitic fluid protein concentration of 15 g/L or more," the researchers concluded. "Norfloxacin may prevent some infections, especially gram-negative bacterial infections, but not the development of [spontaneous bacterial peritonitis] and other noninfectious, liver-related complications."

The study was funded by Programme Hospitalier de Recherche Clinique National 2008 of the French Ministry of Health. Dr. Moreau reported having no conflicts of interest. Two coinvestigators disclosed ties to Gore Norgine, Exalenz, and Conatus.

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SOURCE: Moreau R et al. Gastroenterology. 2018 Aug 22. doi: 10.1053/j.gastro.2018.08.026.

FROM THE AGA JOURNALS

Budesonide tops placebo for lymphocytic colitis

BY AMY KARON
MDedge News

Among patients with lymphocytic colitis, 8 weeks of oral budesonide therapy was associated with significantly higher rates of clinical and histologic remission versus placebo in a multicenter, double-blind clinical trial.

Fully 79% of patients achieved clinical remission with budesonide, compared with only 42% of patients in the placebo arm ($P = .01$), reported Stephan Miehlke, MD, of the Center for Digestive Diseases in Hamburg, Germany, and his associates. A third group of patients received oral mesalazine therapy, which induced clinical remission in 68% of cases ($P = .09$). Budesonide also induced histologic remission significantly more often than did mesalazine (26%; $P = .02$) or placebo (21%; $P = .008$).

"The study population was not large, but the trial was adequately powered," the researchers wrote. The report was published in the December issue of Gastroenterology. "These results confirm the efficacy of budesonide for the induction of remission in active lymphocytic colitis and are consistent with expert recommendations for its use as first-line therapy."

Lymphocytic colitis is a subtype of microscopic colitis that is characterized by an increase in intraepithelial lymphocytes. This condition has substantial negative effects on quality of life – the most common symptom is chronic diarrhea, and some patients also experience fecal incontinence and abdominal pain. Expert guidelines recommend first-line treatment with budesonide and second-line treatment with mesalazine, but evidence supporting either recommendation is sparse and low-quality, the investigators wrote.

For the study, they compared 8 weeks of treatment with pH-modified release oral budesonide granules (9 mg once daily), oral mesalazine granules (3 g once daily), or placebo in 57 patients (19 per arm) with histologically confirmed, newly diagnosed or relapsed lymphocytic colitis. All patients had at least a 12-week history of watery, nonbloody diarrhea, no other documented diarrheal conditions, and no recent history of antidiarrheal therapy. Nearly three-quarters were female and the mean age was 59 years. The primary endpoint was clinical remission, defined as no more than 21 stools in the 7 days before week 8, including no more than 6 watery stools.

After 8 weeks of double-blinded treatment, all clinically remitted patients stopped treatment and were followed for another 16 weeks. Those who were not in remission or who relapsed were offered 4 weeks of open-label budesonide therapy, which led to clinical remission in 88% of cases, the researchers said. "Strikingly, a substantial improvement in symptoms, including a profound reduction in the number of watery stools, was seen within a median of 3 days after starting budesonide therapy."

Serious adverse events were uncommon in all three groups, and each arm had a similar rate of adverse events considered secondary to treatment. In the budesonide group, these included one case each of weight gain, transient ischemic attack, and affective disturbance with sleep disorder. In the mesalazine group, three patients developed acute pancreatitis, increased hepatic enzymes, or dizziness. No patient in any group had a clinically significant shift in cortisol level between baseline and week 8 that was considered related to the study drug," the investigators said. "Other changes in laboratory parameters were not considered clinically relevant in any treatment group."

The study was funded by Dr. Falk Pharma GmbH, Freiburg, Germany. Dr. Miehlke and two coauthors received speaker fees from Dr. Falk Pharma. Dr. Miehlke and one coauthor received consultancy fees from Tillots. One coauthor received speaker fees, has been a member of the advisory board, and has received grants from Tillots.

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SOURCE: Miehlke S et al. Gastroenterology. 2018 Sep 6. doi: 10.1053/j.gastro.2018.08.042.

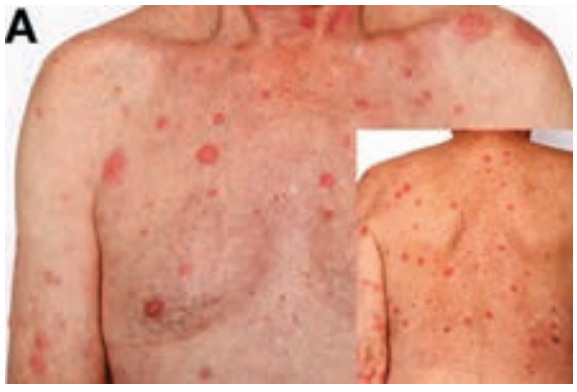
CLINICAL CHALLENGES AND IMAGES

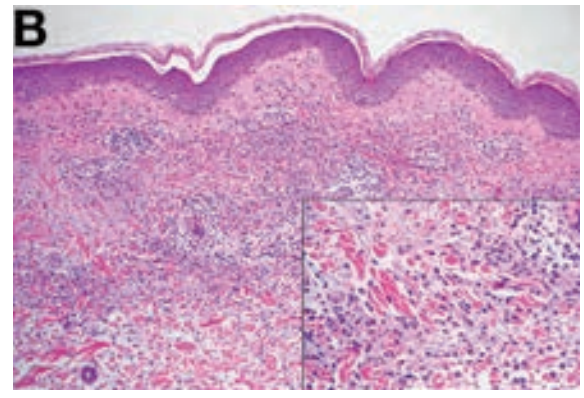
What is your diagnosis?

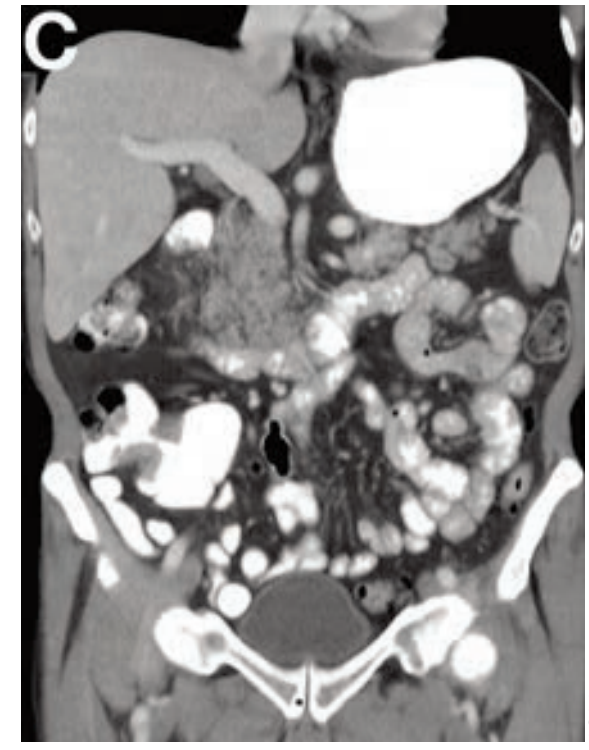
By James H. Tabibian, MD, PhD, Carilyn N. Wieland, MD, and Seth Sweetser, MD. Published previously in Gastroenterology (2016;151[6]:1083-4).

A 65-year-old man presented to the dermatology clinic with a diffuse, multifocal, erythematous rash consisting of nonpruritic papules and plaques on the chest (Figure A) and back (Figure A, inset), which became raised and involved the extremities. He had no significant past medical history, and physical examination was otherwise unremarkable. Laboratory tests were notable for mild anemia and leukocytosis (13×10^9/L). A punch biopsy demonstrated diffuse, dense dermal inflammatory infiltrate composed predominantly of neutrophils, with characteristic dermal edema (Figure B) and bilobed nuclei (Figure B, inset); microbial studies were negative, as were immunostains for lymphoma cutis. Extensive evaluation for potential systemic or other associated conditions was unrevealing, including upper endoscopy and computed tomography enterography; colonoscopy performed 2 years earlier was reportedly unremarkable but with only fair bowel preparation. The patient was prescribed clobetasol ointment and subsequently oral prednisone, both of which yielded prompt improvement; nevertheless, the rash recurred within 1 week of corticosteroid discontinuation. In addition, over the course of the following 6 months, progressive weight loss, periodic fevers, and abdominal distention were noted. Computed tomography of the abdomen was repeated, revealing a new critical finding (Figure C).

See the diagnosis on page 22.







We can't do it without you

A letter from Robert S. Sandler, MD, MPH, AGAF, Chair of the AGA Research Foundation

Dear Colleagues,

As a member of the GI community, you understand the physical, emotional and financial costs of digestive diseases. And you understand the tremendous value of research to advance patient care.

Securing the future of the field is no small task. Talented investigators face significant barriers to enter academic research careers. Not only is there a critical lack of money for entry-level researchers, young investigators are giving up on research careers because funding is scarce.

Gifts to the AGA Research Foundation this year directly supported 41 investigators. Despite this success, over 180 other innovative and promising research ideas went unfunded.

The way we diagnose and treat patients is the results of years of research. **I am asking you to support a cause important to all of us. You can help spark the scientific breakthroughs of today, so clinicians will have the tools to improve care tomorrow.**

Join me in supporting the AGA Research Foundation through a personal gift. Every dollar is a step forward … To new treatments. To cures impacting patients' lives. To new generations of talented investigators in digestive disease research.

Please help us continue our efforts by making your tax-deductible donation. Donate today at www.gastro.org/donate.

Thank you in advance for your support and best wishes for a happy, healthy holiday season and successful New Year.

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MOC update: GI societies and ABIM explore new recertification pathway

AGA is committed to making recertification less burdensome for GIs. After a productive meeting between the GI societies and ABIM, we're hopeful a new, more flexible pathway is on the horizon.

We heard you

The four major physician organizations in gastroenterology and hepatology — AGA, AASLD, ACG and ASGE — share a fundamental commitment to an efficient, clinically relevant and impactful process for the demonstration of ongoing learning and maintenance of specialty board certification for gastroenterologists and hepatologists.

Inspired by our shared objective to create an alternative to the current ABIM 10-year exam and upcoming two-year check-in, the four societies have collaborated to explore alternatives that are less onerous, more relevant, less costly and less time consuming. We look forward to working to achieve this objective for all of GI and hepatology.

Finding a path forward on MOC for GI & hepatology

On Oct. 4, the four societies met with the leadership of ABIM in Philadelphia, Pennsylvania, and presented concepts focusing on a flexible model that can provide a path forward, allowing members of our specialties and subspecialties to focus on knowledge that is relevant to their practice and choose the path that best fits their personal needs.

Continued on following page

AGA's Future Leaders Program receives stellar reviews

Future Leaders alumni and past mentors took to the AGA Community recently to share their experiences with the award-winning program. Now in its third year, the program continues to have an impact on the careers of its participants and AGA.

Here's what they had to say

"The Future Leaders Program provided robust leadership training, valuable mentorship, and invaluable networking with AGA leaders and other AGA members." – **Bryson Katona, MD, MS, PhD**, editor of *The New Gastroenterologist*, University of Pennsylvania

"Through the Future Leaders Program I gained leadership skills, problem-solving skills, and even new research collaborations." – **Jennifer Weiss MD, MS, AGAF,** University of Wisconsin School of Medicine and Public Health

"I think I learned as much from the two outstanding faculty whom I mentored, Jennifer Weiss and Art Beyder, as they did from me!" – **Kim Barrett, PhD, AGAF,** University of California, San Diego (Mentor)

The program is designed for GIs who aspire to further develop their leadership skills with an eye toward serving in a key leadership position both within the field and AGA. Participation from experienced GIs is also critical to the program's success. They are needed to serve as mentors and help develop the next generation of leaders. This is the opportunity to help drive AGA's strategic plan and advance in the field.

Members can access the full discussion: A Fantastic Opportunity: AGA Future Leaders Program in community.gastro.org. Stay tuned to see the list of members selected for the 2019 AGA Future Leaders Program.

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A guide to talking with patients about probiotics

Two recent studies published in *Cell*, "Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features" and "Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT," have received significant media coverage and are causing questions and concern among physicians and patients who use probiotic supplements.

Talking to patients about probiotics

1. Probiotics are generally thought to be safe for healthy individuals, but we don't know the long-term consequences. For individuals who have a chronic disease, are immunocompromised or are otherwise vulnerable (such as the elderly), patients should seek guidance from physicians on whether probiotics may be appropriate. In general, probiotics should not be used indiscriminately; potential risk and benefit should be considered as for all human interventions.
2. This research does not conclude that probiotics are unsafe or useless for everyone. However, the results suggest that individuals may respond very differently to the same probiotic product depending on their diet, genetics, microbiome and other aspects of their health. Experts are trying to better understand which bacteria are best for whom, under which conditions as we transition from an era of empiric medicine to precision medicine.
3. Probiotics currently on the market are foods or dietary supplements. To date, no probiotic products have been approved by the FDA to treat, mitigate, cure or prevent specific diseases.

AGA has recently developed educational materials for patients on probiotics, which can be accessed at www.gastro.org/probiotics in English and Spanish. Share this resource with your patients by printing it out, emailing it, or uploading it to your patient portal.

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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. Severe colitis in asymptomatic patient on screening colonoscopy (http://ow.ly/OBNp30mttPD)
Check out an update on the forum's most popular case, involving a 51-year-old male seen for a screening colonoscopy. Biopsied samples of patchy areas throughout the colon revealed severe active chronic colitis with lymphoplasmacytic infiltrate, crypts and crypt abscesses, and no granulomas.

2. Paraplegic colonic gas (http://ow.ly/ChNM30mtEia)
Symptoms started 2 years ago for this 28-year-old paraplegic male, who was hospitalized with multiple episodes of postprandial abdominal bloating and pain. He has a permanent catheter and is on a diet mostly of meat and specific vegetables. His physician solicited the community for help with management of colonic gas and symptoms.

3. Small submucosal nodule and gastric intestinal metaplasia (http://ow.ly/Qqii30mtEpo)
The physician needs advice on next steps for a 55-year-old female who had an EGD for dyspepsia. Biopsies of a 1-cm nodule and surrounding areas revealed moderate chronic inactive gastritis with focal intestinal metaplasia and reactive hyperplastic changes with no dysplasia.

4. Perianal Crohn's preceding luminal disease (http://ow.ly/GHV430mtEwo)
This extensive case of a 16-year-old female started with severe constipation, until she developed a painful abscess on the right perianal region. Perianal fistula with abundant granulation tissue and mucoid discharge was noted, and biopsies revealed inflammation with fibrosis, giant cell reaction, and granulomatous inflammation. This past summer, an MR enterography and pelvic MRI revealed a small right perianal intersphincteric fistula with possible drainage through the skin.

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

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Continued from previous page

The GI societies and ABIM agreed to work together to explore the development of a third option for MOC.

Guided by core principles
In working together to develop an alternative to MOC, the four GI societies are guided by these core principles embraced by our organizations several years ago:

- MOC needs to be simpler, less intrusive and less expensive.
- We continue to support alternatives to the high-stakes, every-10-year recertification exam.
- We do not support single source or time-limited assessments, as they do not represent the current realities of medicine in the digital age.
- We support the concept that, for the many diplomates who specialize within certain areas of gastroenterology and hepatology, MOC should not include high-stakes assessments of areas in which the diplomate may not practice.
- We support the principles of lifelong learning, as evidenced by ongoing CME activities, rather than lifelong testing.

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DDSEP eight

Quick quiz answers

Q1. Correct Answer: A

Rationale
This patient has solitary rectal ulcer syndrome. Defecography is useful for determining the presence of intussusception, mucosal prolapse, nonrelaxing puborectalis muscle and incomplete or delayed rectal emptying. The importance of this would be to suggest possible therapy, such as biofeedback for dyssynergia. Rectal suction biopsies would be useful for possible Hirschsprung's disease, which is unlikely in this case. Colonic transit testing is useful for evaluation of slow transit constipation and is not indicated in this case. The histopathology of solitary rectal ulcer syndrome is characteristic with fibromuscular obliteration of the lamina propria. There is no indication for evaluation of inflammatory bowel disease, therefore answers D and E are incorrect.

References/Remediation Tools
1. Chiang JM, Changchien CR, Chen JR. Solitary rectal ulcer syndrome: an endoscopic and histological presentation and literature review. Int J Colorectal Dis. 2006;21:348-56.
2. Zhu QC, Shen RR, Qin HL, Wang Y. Solitary rectal ulcer syndrome: clinical features, pathophysiology, diagnosis and treatment strategies. World J Gastroenterol. 2014 Jan 21;20(3):738-44.

Q2. Correct Answer: D

Rationale
This patient fulfills Rome III criteria for IBS-D. A recent technical review critically evaluated the existing evidence for the various available treatments of IBS-D. Based on the evaluation of existing evidence, this review concluded that alosetron and rifaximin can be recommended (over no drug treatment) for the treatment of IBS-D. Additionally, the review concluded that TCAs and antispasmodics can be recommended (over no drug treatment) for the treatment of IBS in selected patients with no contraindications. To date, probiotics are not routinely recommended for the treatment of IBS. Further studies are needed to determine the role of probiotics in the management of IBS.

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Longer stays link to readmissions

Cirrhosis *from page 1*

In a retrospective cohort study, Dr. Umapathy and colleagues identified 230,036 patients from the Healthcare Cost and Utilization Project National Readmission Database for 2014 who had been discharged with a diagnosis of cirrhosis; of these patients, there were 185,737 index cases after excluding readmissions. Included patients had a mean age of 60.2 years and mean length of stay of 6.4 days, with 46% of patients having a length of stay longer than 4 days and mean total charges of $56,519. With regard to cirrhosis, 55% of patients displayed cirrhosis complications and 6.7% had more than three cirrhosis-related complications; the most common complication was ascites, in 32% of patients.

Length of stay longer than 4 days (0.84; *P* less than .001) and variceal hemorrhage (0.74; *P* = .002) were associated with reduced risk of readmissions at 30 days.

Overall, 11.09% of patients were readmitted at 30 days and 18.74% of patients were readmitted at 90 days, Dr. Umapathy said. Patients were more likely to be readmitted at 30 days if they were originally admitted on a weekend (adjusted prevalence ratio, 1.06; *P* = .001); were in a medium (1.09; *P* = .009) or large (1.11; *P* less than .001) hospital; were admitted at a metropolitan teaching hospital (1.07; *P* less than .001); were insured by Medicaid (1.07; *P* less than .001); or were transferred to an extended care (1.51; *P* less than .001) facility or discharged to home health care (1.43; *P* less than .001).

Compared with patients who were not readmitted at 30 days, patients with 30-day readmission had a higher rate of alcoholic liver disease (43% vs. 46%; *P* less than .001), hepatitis C (28% vs. 32%; *P* less than .001), ascites (31% vs. 43%; *P* less than .001), hepatic encephalopathy (15% vs. 22%; P less than .001), hepatorenal syndrome (2.3% vs. 4.9%; *P* less than .001), hepatocellular cancer (5.1% vs. 5.7%; *P* = .001), presence of any cirrhosis complications (54% vs. 65%; *P* less than .001), and presence of more than three cirrhosis-related complications (6.3% vs. 10%; *P* less than .001). When adjusted in a multivariate analysis, association with readmission at 30 days for patients with cirrhosis-related complications such as ascites (1.42; *P* less than .001), hepatic encephalopathy (1.44; *P* less than .001), and hepatorenal syndrome (1.34; *P* less than .001) remained, Dr. Umapathy noted.

Length of stay longer than 4 days (0.84; *P* less than .001) and variceal hemorrhage (0.74; *P* = .002) were associated with reduced risk of readmissions at 30 days. "Focus on length of stay may result in patients being discharged prematurely, leading to higher early readmission," Dr. Umapathy said.

Dr. Umapathy reports no relevant conflicts of interest.

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SOURCE: Umapathy C et al. ACG 2018, Presentation 60.

Hep C–infected livers are safe for transplant

BY JIM KLING
MDedge News

SAN FRANCISCO – A new analysis shows that hepatitis C–infected livers can be safely transplanted into recipients with no effect on graft survival, retransplantation, or mortality. The work confirms that readily available direct-acting antiviral therapy can protect organ recipients and open a source of organs that is typically overlooked.

The work should encourage both physicians and patients to take a closer look at hepatitis C–infected organs, especially for sicker patients, according to Sonali Paul, MD, who presented the study at the annual meeting of the American Association for the Study of Liver Disease 2018.

"A lot of people have an ethical issue with it because we're actively transplanting a virus into someone. We're giving someone a disease. My take on it is that we give people Epstein Barr virus or cytomegalovirus all the time – we just [provide] prophylaxis against it, and we don't even bat an eye. Hepatitis C can be devastating, but we have totally effective treatments for it," said Dr. Paul, who is an assistant professor of medicine at the University of Chicago.

She cited one colleague at the University of Chicago who several years ago transplanted an organ that had been passed over 700 times, though times have changed since then. "I think people more and more are doing this practice because we know it's so successful," said Dr. Paul.

Jim Kling/MDedge News

Dr. Sonali Paul

It's also cost effective. Another study, presented during the same session by Jag Chhatwal, PhD, assistant professor at Harvard Medical School, Boston, showed that accepting a hepatitis C–positive liver is cost effective in patients with Model for End-Stage Liver Disease (MELD) scores ranging from 22 to 40.

"I think we're going to find across all organ systems, if we can transplant patients rather than keep them on dialysis or keep them on wait lists, it's got to be cost effective, especially if you think of the health care–associated costs – like a heart transplant patient waiting on the list in the ICU. That's a huge health care cost," said Dr. Paul.

Dr. Paul's team performed an analysis of the Scientific Registry of Transplant Recipients, including single organ transplants from deceased donors, during 2014-2018. Over that period, the number of transplants from hepatitis C–positive donors to hepatitis C–positive recipients rose from 8 in 2014 to 269, and the number of transplants from hepatitis C–positive donors to hepatitis C–negative recipients rose from 0 to 46.

The researchers compared trends from hepatitis C–negative donors with hepatitis C–negative recipients (n = 11,270), negative donors with positive recipients (n = 4,748), positive donors with negative recipients (n = 87), and positive donors with positive recipients (n = 753). Donor status had no effect on graft survival times at 1 or 2 years, with values ranging from 92.6% (negative to negative) to 94.3% (positive to positive) at 1 year and between 85.7% (positive to negative) and 89.7% (positive to positive) at 2 years.

"For someone who has a MELD score of over 20, who has a declining quality of life and really can't do anything, I think this is a great opportunity. And most patients are absolutely willing to take these organs. We haven't had many people say no, especially if they feel poorly," said Dr. Paul.

'I think we're going to find across all organ systems, if we can transplant patients rather than keep them on dialysis or keep them on wait lists, it's got to be cost effective, especially if you think of the health care–associated costs.'

She also underscored the importance of ensuring that the patient is informed of the status of the donor liver and the need to complete treatment: "The patient has to know what's happening, and the hospital has to have a safety net if the insurance doesn't pay for hepatitis C treatment."

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SOURCE: Paul S. AASLD 2018, Abstract 0249.

Risk of cancer in NAFLD is 91% higher than in control subjects

BY DOUG BRUNK
MDedge News

SAN FRANCISCO – The risk of malignancy among patients with nonalcoholic fatty liver disease (NAFLD) is 91% higher than it is among age- and sex-matched control subjects, with gastrointestinal sites being the most commonly affected.

Those are key findings from a community cohort study with up to 21 years of follow-up, which one of the authors, Alina M. Allen, MD, discussed during a press briefing at the annual meeting of the American Association for the Study of Liver Diseases.

"NAFLD is the most common chronic liver disease in the Western world," said Dr. Allen, a gastroenterologist at the Mayo Clinic, Rochester, Minn. "It affects one in four adults in the U.S. It is related to fat accumulation in the liver in people who are overweight or obese and can lead to cirrhosis and liver-related mortality. However, the most common cause of death in this population is not liver disease but malignancy and cardiovascular disease. There is a paucity of epidemiologic studies of extrahepatic cancer in NAFLD. It is not clear what types of cancers and how much higher their cancer risk is in reference to the general population."

In an effort to determine the incidence of cancer diagnoses in NALFD, compared with controls, in a U.S. community, Dr. Allen and her colleagues drew from the Rochester Epidemiology Project to evaluate 4,791 adults diagnosed with NAFLD and 14,432 age- and sex-matched control subjects in Olmstead County, Minn., during 1997-2017. The researchers obtained corresponding Surveillance, Epidemiology, and End Results Program (SEER) rates as a quality check and used a regression model to assess the malignancy risk in NAFLD overall and by cancer type, age, sex, and body mass index. They recorded

Doug Brunk/MDedge News

Dr. Alina M. Allen

all new diagnoses of cancers that developed in both groups until 2018, for a total possible follow-up of 21 years, and they reported results in incidence rate ratios, a risk estimate similar to hazard ratios.

The mean age of the study population was 53 years, 53% were female, and the mean follow-up was 8 years with a range from 1 to 21 years. New cancers were identified in 16% of subjects with NAFLD and in 12% of control subjects. The overall risk of malignancy was 91% higher in NAFLD subjects, compared with control subjects; there were higher rates in the NAFLD subjects for most types of cancers, but the largest increases were in GI cancers. The greatest malignancy risk was for cancer of the liver (RR, 3.24), followed by cancer of the uterus (RR, 2.39), stomach (RR, 2.34), pancreas (RR, 2.09), and colon (RR, 1.75). "Interestingly, the risk of colon cancer increased only in men but not in women," Dr. Allen said. "These data provide an important hierarchical overview of the top most important malignancy risks associated with NAFLD that the medical community should be aware of."

When the researchers looked for differences in age at cancer diagnosis between NAFLD and controls, they found that pancreas cancer occurred at a younger age among subjects with NAFLD. They also observed that colon cancer occurred at a younger age in men with NAFLD, but not in women with the disease. "What was most interesting to us was the assessment of cancer risk in NAFLD versus obesity alone," Dr. Allen said. "Previous studies from the general population have linked obesity to a higher risk of cancer. Whether the presence of fatty liver disease would impact that risk has not been assessed. We showed that obesity is associated with a higher risk of cancer only in those with NAFLD, not in those without. If validated in independent cohorts, these findings could change our understanding of the relationship between obesity and cancer and the importance of screening for NAFLD – not only to risk-stratify liver disease but also for the risk of extrahepatic malignancy."

Dr. Allen concluded her presentation by noting that findings from large population-based studies such as the Rochester Epidemiology Project "can offer important epidemiologic data regarding the biggest threats to the health of a community," she said. "Such data increase awareness, enable appropriate counseling, and could inform screening policies. There is a signal in the fact that the GI cancers are increased [in NAFLD]. It's an interesting signal that needs to be studied further."

Dr. Allen reported having no financial conflicts.

dbrunk@mdedge.com

SOURCE: Allen AM. Hepatol. 2018;68[S1]: Abstract 31.

U.S. death rates from chronic liver disease continue to rise

BY DOUG BRUNK
MDedge News

SAN FRANCISCO – Chronic liver disease mortality continues to rise in the United States, driven largely by a spike in nonalcoholic fatty liver disease (NAFLD), according to results from an analysis of national data.

"I believe it's all related to a big increase in obesity and type 2 diabetes in this country," lead study author Zobair M. Younossi, MD, MPH, said in an interview in advance of the annual meeting of the American Association for the Study of Liver Diseases. "Those two risk factors drive NAFLD and its progressive type, nonalcoholic steatohepatitis (NASH). That accounts for at least part of the increase in mortality related to liver disease."

In an effort to evaluate recent mortality trends in chronic liver disease in the United States, Dr. Younossi and his colleagues drew from National Vital Statistics Data during 2007-2016. They used ICD-10 codes to select mortality data for alcoholic liver disease, chronic hepatitis B and C, iron overload, NAFLD, cirrhosis, and hepatocellular carcinoma. NAFLD cases were defined as those having an ICD-10 code for NAFLD/NASH or an ICD-10 code for "cirrhosis of unknown etiology." Next, the researchers adjusted age-standardized death rates to the 2000 U.S. Census population and used logistic regression and propensity scores to estimate predictors of chronic liver disease–related deaths.

Dr. Younossi, who chairs the department of medicine at Inova Fairfax Medical Campus in Falls Church, Va., and his colleagues reported findings from 838,809 chronic liver disease–related deaths during the study period. They found that the age-standardized death rate for chronic liver disease increased from 21.9/100,000 population in 2007 to 24.9/100,000 population in 2016, which translated into an annual percentage change of 1.3% for males and 2.5% for females. Chronic liver disease–related deaths increased with age and were highest among those aged 55-64 years, followed by those aged 65-74 years – an average annual percentage change of 3.4% and 3.1% in each group.

Among chronic liver disease–related deaths, the most common diagnostic etiology was NAFLD (34.7%), followed by alcoholic liver disease (28.8%) and chronic hepatitis C (21.1%). Between 2007 and 2016, death rates increased from

Continued on page 20

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*This product has been discontinued.

Continued from page 20

7.6 to 9.0 per 100,000 population for NAFLD (an average annual percentage change of 2.1%) and from 6.1 to 7.9 per 100,000 population for alcoholic liver disease (an average annual percentage change of 3.1%). "What surprised me was that, despite highly effective treatment for HCV, we still have a burden of hepatitis C in this country," Dr. Younossi said. "It's still the most common cause of liver disease in the U.S. But it seems like hepatitis C–related liver disease is being replaced quickly by liver disease from nonalcoholic steatohepatitis. This transition between hepatitis C as the most important cause of liver disease and liver mortality to NASH or obesity-related NASH is becoming more rapid than I expected."

On multivariate analysis, three factors were independently associated with an increased risk of death in NAFLD: the presence of type 2 diabetes (odds ratio, 1.78), cardiovascular disease (OR, 1.07), or renal failure (OR, 1.08).

"One important message from this study is that NASH is very common in the U.S. population," said Dr. Younossi, who is also a professor of medicine at Virginia Commonwealth University, Richmond. "These patients are underrecognized and underdiagnosed because they are asymptomatic. The second message is that there is a subtype of patients with fatty liver disease – even a subtype of NASH – that can progress to cirrhosis and its complications. We have to pay attention to this silent disease to identify patients who are at risk for progressive liver disease and try to address some of the risk issues, such as tight control of diabetes, obesity, and control of hypertension and hyperlipidemia. Short of that, right now we have very few medical treatments such as vitamin E and pioglitazone recommended for a very selected group. In contrast, there are plenty of new medications that are being developed. The first step in tackling this disease is to identify who the patients are with fatty liver disease who are at risk for bad outcomes and make sure they're linked to care by a knowledgeable caregiver [who] understands the importance of NASH."

Dr. Zobair M. Younossi

Dr. Younossi acknowledged certain limitations of the study, including the fact that liver disease diagnoses were based on ICD-10 coding. He disclosed that he is a consultant for Gilead, Intercept, Novo Nordisk, BMS, AbbVie, Viking, Term Quest Diagnostics, Echosens,and Shionogi. He has also received grant/research support from Gilead, Intercept, and BMS.

dbrunk@mdedge.com

SOURCE: Hepatol. 2018;68(S1): Abstract 763.

High rates of prescription opioid, benzodiazepine use observed in chronic liver disease

BY DOUG BRUNK
MDedge News

SAN FRANCISCO – Patients with chronic liver disease are prescribed opioids and benzodiazepines at very high rates, despite risk for adverse consequences because of hepatic metabolism, according to results from a large longitudinal study of national data.

"Middle-aged individuals and those with a background of substance abuse and mental health conditions appear to have highest rates of use and represent populations for which targeted interventions to curb use could be highest yield," lead study author Monica Konerman, MD, said in an interview in advance of the annual meeting of the American Association for the Study of Liver Diseases.

In an effort to better understand the rates of prescription opioid and benzodiazepine use in chronic liver disease, Dr. Konerman, director of the Michigan Medicine NAFLD Clinic at the University of Michigan, Ann Arbor, and her colleagues drew from the Truven Health Analytics Marketscan databases from 2009 to 2015. They limited the analysis to individuals with drug coverage who had chronic hepatitis C (HCV) without cirrhosis, cirrhosis, congestive heart failure (CHF), or chronic obstructive pulmonary disease (COPD), and examined pharmacy files for outpatient prescriptions.

Dr. Konerman reported data from 210,191 patients with HCV, 79,332 with cirrhosis, 766,840 with CHF, and 1,438,798 with COPD. Their median age was 59 years, and 51% were female. In per person-years, the prevalence of prescription opioid use was 25% in patients with chronic HCV, 53% in patients with cirrhosis, 26% in those with CHF, and 24% in those with COPD. At the same time, in person-years, the prevalence of benzodiazepine use was 12% in patients with chronic HCV, 21% in patients with cirrhosis, 12% in those with CHF, and 13% in those with COPD. Use of opioids was greatest in adults 40-59 years of age (*P* less than .001). High-dose opioid use, defined as 100 opioid morphine equivalents per day or greater, occurred in 23% of those with cirrhosis and in 22% of those with HCV.

Dr. Konerman acknowledged "inherent limitations to studies that are secondary database analyses that rely on diagnosis codes for categorization of disease with potential for both over and under classification. We also did not capture inpatient prescriptions," she said.

Dr. Konerman reported having no financial disclosures.

dbrunk@mdedge.com

Dose-response relation observed

Etrasimod *from page 1*

tically significant and clinically meaningful differences in all of the primary and secondary endpoints, and most exploratory endpoints were also significantly proved," William J. Sandborn, MD, AGAF, FACG, professor of clinical medicine at the University of California, San Diego,

'The OASIS trial results for etrasimod would support proceeding to a phase 3 program for this drug in patients with moderate to severe ulcerative colitis.'

stated in his presentation at the meeting. "A dose-response relationship was observed in virtually all of the measures of treatment efficacy."

The abstract received the ACG Auxiliary Award (Member), which is given to ACG members each year with outstanding abstract submissions.

Dr. Sandborn and his colleagues enrolled 156 patients with ulcerative colitis (UC) into the OASIS study, a randomized, double-blind, parallel-group, phase 2 study of etrasimod, an oral sphingosine 1-phosphate (S1P) receptor modulator, compared with placebo. Patients were aged 18-80 years, with moderate to severe UC as defined by a three-component Mayo Clinic Score (MCS) comprising rectal bleeding, frequency of stool, and endoscopy.

Those patients who achieved an MCS score between 4 and 9 points with an endoscopic subscore of at least 2 and rectal bleeding (RB) subscore of at least 1 were included. Patients were divided into once-daily etrasimod 1 mg (52 patients), once-daily etrasimod 2 mg (50 patients), and placebo (54 patients) groups and treated over a 12-week period.

At 12 weeks, the least-squares mean difference for change in baseline in three-component MCS was 1.94 in the 1-mg etrasimod group and 2.49 in the 2-mg etrasimod group compared with placebo (1.50). Endoscopic improvement was greater in the 1-mg etrasimod (22.5%) and 2-mg (41.8%) groups compared with placebo (17.8%); endoscopic remission rates also improved in the 1-mg etrasimod (13.7%) and 2-mg (15.3%) groups compared with placebo (5.3%). Lymphocyte count circulation significantly decreased in the 1-mg etrasimod (37.2%) and 2-mg (57.3%) groups compared with the placebo group. With regard to rectal bleeding, the rectal bleeding subscore also decreased in the 1-mg etrasimod and 2-mg groups compared with placebo at 12 weeks from baseline.

Jeff Craven/MDedge News

Dr. William J. Sandborn

The researchers noted no significant differences in adverse events among groups, with the placebo group showing a higher rate of major adverse events (11.1%) compared with the 1-mg etrasimod (5.8%) and 2-mg etrasimod (0%) groups.

"The OASIS trial results for etrasimod would support proceeding to a phase 3 program for this drug in patients with moderate to severe ulcerative colitis," Dr. Sandborn concluded.

Dr. Sandborn reports consultancies, speaker bureau memberships, and research support from AbbVie, Biogen, Celgene, Ferring, Genentech, Gilead Sciences, Immune Pharmaceuticals, Janssen, Lilly, MedImmune, Novartis, Pfizer, Regeneron, Ritter Pharmaceuticals, Salix, Theradiag, UCB Pharma, and Vascular Biogenics, among others.

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SOURCE: Sandborn WJ et al. ACG 2018, Presentation 11.

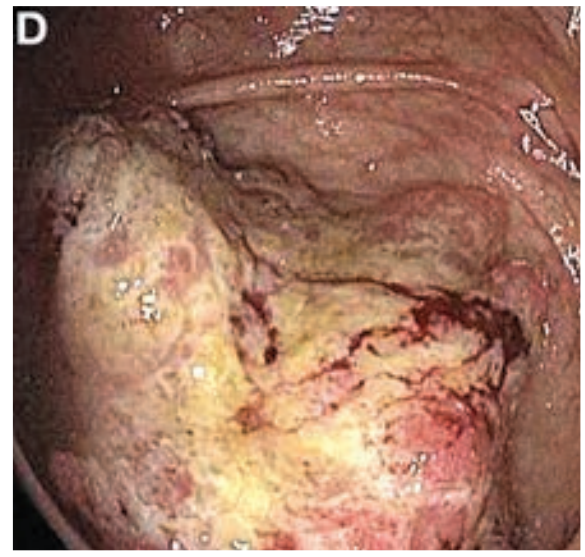
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 14: Cecal carcinoma–associated paraneoplastic Sweet's syndrome

Based on the tomographic appearance of an "apple core"–like lesion in the right lower quadrant, the patient was referred for colonoscopy, which revealed a malignant-appearing cecal mass (Figure D), with biopsies confirming adenocarcinoma; despite these findings, no bowel-related symptoms were reported. The patient underwent laparoscopic right hemicolectomy, after which the skin lesions began to resolve, and corticosteroids were successfully tapered. The overall presentation was consistent with Sweet's syndrome, with a paraneoplastic etiology being favored given the clinical scenario, including absence of alternative etiologies and dependence on corticosteroids for control of skin disease until resection of the underlying malignancy was performed.

Sweet's syndrome was first described in a case series of eight patients published in 1964 by the English dermatologist Dr. Robert Douglas Sweet.[1,2] Sweet's syndrome is characterized by fever, neutrophilia, and sterile erythematous plaques or nodules, which most commonly involve the upper extremities and face and respond to corticosteroid therapy. It may be malignancy associated, drug induced, autoimmune disease related, or idiopathic.[2,3] The pathogenesis of Sweet's syndrome is unclear, but T-lymphocyte, neutrophil chemotaxis, and cytokine (e.g., interleukin-6 and granulocyte colony–stimulating factor) abnormalities have been suggested.[2] Diagnosis is based on the clinical presentation and context together with typical dermatopathologic findings, including a dense neutrophilic infiltrate. Skin lesions may be phasic, but persist typically until appropriate therapy (e.g., corticosteroids, chemotherapy) is administered or the offending drug removed. Malignancy-associated (i.e., paraneoplastic) Sweet's syndrome accounts for approximately 20% of all cases; these primarily involve hematologic malignancies, most commonly leukemia, but adenocarcinomata have also been implicated.[3] Recurrence of Sweet's syndrome can occur and often heralds relapse of the underlying disease.



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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

FDA approves adalimumab biosimilar Hyrimoz

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has approved the adalimumab biosimilar Hyrimoz (adalimumab-adaz) for a variety of conditions, according to Sandoz, the drug's manufacturer and a division of Novartis.

FDA approval for Hyrimoz is based on a randomized, double-blind, three-arm, parallel biosimilarity study that demonstrated equivalence for all primary pharmacokinetic parameters, immunogenicity, and safety, according to the press release.

A second study confirmed therapeutic equivalence in patients with moderate to severe plaque psoriasis, with Hyrimoz having a safety profile similar to that of adalimumab. Hyrimoz was approved in Europe in July 2018.

Hyrimoz has been approved to treat adult Crohn's disease, ulcerative colitis, rheumatoid arthritis, juvenile idiopathic arthritis in patients aged 4 years and older, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. The most common adverse events associated with the drug, according to the label, are infections, injection-site reactions, headache, and rash.

Hyrimoz is the third adalimumab biosimilar approved by the FDA.

"Biosimilars can help people suffering from chronic, debilitating conditions gain expanded access to important medicines that may change the outcome of their disease. With the FDA approval of Hyrimoz, Sandoz is one step closer to offering U.S. patients with autoimmune diseases the same critical access already available in Europe," Stefan Hendriks, global head of biopharmaceuticals at Sandoz, said in the press release.

Find the full press release on the Novartis website.

lfranki@mdedge.com

AGA Resource
AGA is taking the lead in educating health care providers and patients about biosimilars and how they can be used for IBD patient care. Learn more at www.gastro.org/biosimilars.

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Endocuff decreases withdrawal time but not detection rate during colonoscopy

BY JEFF CRAVEN
MDedge News

PHILADELPHIA – Use of a device on the distal end of a colonoscope to expand the view of the colon lowered the mean inspection time during colonoscopy without significantly reducing adenoma or sessile serrated polyp detection rate, according to a presentation at the annual meeting of the American College of Gastroenterology.

"The finger projections on the tip of the Endocuff can engage the colonic folds, and that allows us to see the proximal sides of these folds," Seth A. Gross, MD, AGAF, chief of gastroenterology at NYU Langone Health Tisch Hospital in New York, said in his presentation. "It also changes topography and temporarily stretches different segments of the colon depending on where you are to help expose more surface area and ultimately identify more polyps."

Dr. Gross and his colleagues analyzed the withdrawal time of colonoscopy with the Endocuff Vision (Olympus, Center Valley, Pa.) in 101 patients, compared with withdrawal time during a standard colonoscopy in 99 patients as measured by stopwatch. Other endpoints in the study included insertion time, adenoma detection rate (ADR), sessile serrated polyp detection (SSPD), and number of adenomas and sessile serrated polyps per colonoscopy. Patients were included if they were at least 40 years old with a screening, surveillance, or diagnostic indication for colonoscopy; they were excluded if they had inflammatory bowel disease, polyposis syndrome, prior colon resection, prior colorectal polyp or cancer, previous incomplete colonoscopy, or severe diverticular disease.

DR. GROSS

Inspection time in the Endocuff group was 6.3 minutes, compared with 8.2 minutes in the standard colonoscopy group (*P* less than .001), and insertion time was 9.9 minutes in the Endocuff group, compared with 11.3 minutes in the standard colonoscopy group. A multivariate analysis showed the shorter inspection times in the Endocuff group remained significant (*P* less than .0001).

In the Endocuff group, ADR was 61.4% with 1.43 adenomas per colonoscopy, while the standard colonoscopy group had an ADR of 52.5% with an adenoma detection rate of 1.07 per colonoscopy. SSPD was 19.8% in the Endocuff group and 11.1% in the standard group, with a SSPD per colonoscopy of 0.27 and 0.21, respectively.

The study was unblinded, and there were two endoscopists performing the procedures, which raises the question of whether the results could be generalized to other gastroenterologists, Dr. Gross noted.

"We recommend that future studies that are meant to be powered for adenoma detection rate and sessile serrated lesions be done to sort of validate this, and probably have

Continued on following page

No difference for blacks vs. whites in precancerous colorectal neoplasm prevalence: A meta-analysis

BY ANDREW D. BOWSER
MDedge News

Rates of advanced precancerous neoplasia did not differ between average-risk black and white individuals who underwent screening colonoscopy in a recent meta-analysis, prompting investigators to suggest that the age at which screening starts need not differ based on race.

There was also no difference in advanced neoplasia in the proximal colon between black and white screen-eligible individuals in the most rigorous of the studies included in the meta-analysis, investigators reported.

Those findings support eliminating the age difference at which to begin screening of average-risk individuals, as is currently recommended in some guidelines, said Thomas F. Imperiale, MD, AGAF, the Lawrence Lumeng Professor of Gastroenterology and Hepatology at Indiana University, Indianapolis, and his coinvestigators.

In areas with no disparities in screening access, average-risk screening could begin at age 50 years, regardless of race, at least based on results of this meta-analysis, Dr. Imperiale and his colleagues said in their report.

"To the extent that advanced adenoma is the precursor lesion for colorectal cancer, tailoring the age at which to begin screening and how to screen based on race is not supported by our findings," they said in the report, which appears in the journal Gastroenterology.

Dr. Imperiale and his coinvestigators scanned the medical literature and identified nine studies looking at the prevalence of advanced adenomas or advanced precancerous colorectal neoplasms in both black and white individuals of average risk who had undergone screening colonoscopy.

Those nine cross-sectional studies, all published during 2010-2017, represented a total of 302,128 participants. Six studies were of high methodologic quality and had a low risk of bias, while the remaining three failed to adjust for age and sex, authors of the meta-analysis said in their report.

Given these findings, the higher colorectal cancer incidence and mortality seen in black adults is less likely because of biology, and more likely from differences in symptom recognition, diagnostic evaluation, or acceptance of preventive services.

Prevalence of advanced adenomas or advanced precancerous colorectal neoplasms ranged from 2% to 10% for whites and from 5% to 12% for blacks in the nine studies, with only one study, which had no histology results available, showing a higher prevalence in blacks, investigators found.

Taken together, there was no difference between racial groups, with a point prevalence of 6.57% for blacks and 6.20% for whites (odds ratio, 1.03; 95% confidence interval, 0.81-1.30) and an absolute risk difference of zero, according to the statistical analysis.

Of five studies that included data on proximal advanced adenomas or advanced precancerous colorectal neoplasms, two showed a greater prevalence in blacks versus whites, with point prevalences of 3.30% and 2.42%, respectively. However, there was no difference in prevalence for the "best subset" of three studies with a moderate degree of heterogeneity, investigators said.

Given these findings, the higher colorectal cancer incidence and mortality seen in black adults is less likely because of biology, and more likely from differences in symptom recognition, diagnostic evaluation, or acceptance of preventive services, Dr. Imperiale and his coauthors said in a discussion of the results.

Some current guidelines suggest starting colorectal cancer screening at age 40 years for average-risk blacks, which is 5-10 years earlier than for nonblacks, investigators said, though of note, the most recent American Cancer Society recommendations recommend screening starting at age 45 years for all average-risk individuals.

"If this recommendation is followed broadly, it would lessen the clinical and policy implications of our findings," they wrote. "However, the uptake of this recommendation is yet to be determined, as it differs from those of all other professional organizations."

The study was supported by Indiana CTSI Collaboration in Translational Research Grants. Dr. Imperiale and his coauthors reported no conflicts of interest.

ginews@gastro.org

SOURCE: Imperiale TF et al. Gastroenterology. 2018 Aug 21. doi: 10.1053/j.gastro.2018.08.020.

more endoscopists involved in a study like this," Dr. Gross said. "But this is the start of an interesting conversation where one could be more efficient without sacrificing our detection rate for both adenomas and sessile serrated lesions."

Dr. Gross reports a consultancy with Olympus.

ginews@gastro.org

SOURCE: Gross SA et al. ACG 2018, Presentation 37.

Trump scheme for Part B drugs raises red flags

BY GREGORY TWACHTMAN
MDedge News

A proposed Trump administration plan for paying for drugs under Medicare Part B has raised red flags for doctors.

The Centers for Medicare & Medicaid Services announced Oct. 25 that it will test paying for Part B drugs by more closely aligning those payments with international rates.

The so-called International Price Index (IPI) model "would test whether increasing competition for private-sector vendors to negotiate drug prices, and aligning Medicare payments for drugs with prices that are paid in foreign countries, improves beneficiary access and quality of care while reducing expenditures," according to a government fact sheet.

Under the test, private vendors would "procure drugs, distribute them to physicians and hospitals, and take on the responsibility of billing Medicare. Vendors would aggregate purchasing, seek volume-based discounts, and compete for providers' business, thereby creating competition where none exists today."

Health care professionals and hospitals in certain geographic areas would receive their Part B drugs under this program, while the rest of the country would continue under the current buy-and-bill system. Eventually, over the 5-year phase-in period, half of the geographic regions would fall under this IPI model.

CMS officials note that the IPI model "would maintain beneficiaries' choice of provider and treatments and would have meaningful beneficiary protections such as enhanced monitoring and Medicare Beneficiary Ombudsman supports."

Initially, only single-source drugs and biologics with available international pricing data would be provided under the IPI model, which could be expanded over time to include drugs available via multiple sources.

Currently, Medicare typically pays average sales price (ASP) plus a 6% add-on for drugs under Part B. Under IPI, if the international price is determined to be lower than the ASP, the CMS would reimburse based on a target price derived from an international price index, with the hope that manufacturers would match the international price. The target price would be phased in over a 5-year period.

The plan also calls for an add-on price similar to the current buy-and-bill system; however, the CMS aims to bring the add-on back to 6% rather than the actual 4.3% under the budget sequestration.

Other add-ons are also under consideration, such as paying a fixed amount per encounter or per month as well as a unique payment based on drug class, physician specialty, or physician practice.

The American Gastroenterological Association also has concerns, noting that the proposed changes in policy are complex and certain details are lacking, which makes it difficult to assess fully the impact of the proposal.

While it's true that the high cost of biologics, such as those used to treat inflammatory bowel disease, create barriers to patient access, efforts to address costs may create other patient access issues and penalize gastroenterologists for providing high-quality care to some of the most complex patients. The Competitive Acquisition Program previously abandoned created patient access issues. Moreover, utilization management strategies such as step therapy or "fail first" protocols have no place in the Medicare Part B program. Policy makers should be careful to not penalize Medicare patients who depend on timely access to needed therapies.


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"The administration's proposal for an International Pricing Index Model for Part B drugs raises a number of questions, and we need to have a greater understanding of the potential impact of the proposal on patients, physicians, and the health care system," American Medical Association President Barbara McAneny, MD, said in a statement. "We look forward to working constructively with the Administration as it seeks feedback."

Comments are due Dec. 24. The CMS plans to issue the proposed rule related to this model in the spring of 2019.

gtwachtman@mdedge.com

Guideline authors inconsistently disclose conflicts

BY HEIDI SPLETE
MDedge News

Financial conflicts are often underreported by authors of clinical practice guidelines (CPGs) in several specialties including oncology, rheumatology, and gastroenterology, according to a pair of research letters published in JAMA Internal Medicine. The Institute of Medicine recommends that guideline authors include no more than 50% individuals with financial conflicts.

In one research letter, Rishad Khan, BSc, of the University of Toronto in Ontario and his colleagues reviewed data on undeclared financial conflicts of interest among authors of guidelines related to high-revenue medications.

The researchers identified CPGs via the National Guideline Clearinghouse and selected 18 CPGs for 10 high-revenue medications published between 2013 and 2017. Financial conflicts of interest were based on the Centers for Medicare & Medicaid Services Open Payments.

Of the 160 authors involved in the various guidelines, 79 (49.4%) disclosed a payment in the CPG or supplemental materials, and 50 (31.3%) disclosed payments from companies marketing 1 of the 10 high-revenue medications in the related guidelines.

Another 41 authors (25.6%) received but did not disclose payments from companies marketing 1 of the 10 high-revenue medications in CPGs.

Overall, 91 authors (56.9%) were found to have financial conflicts of interest that involved 1 of the 10 high-revenue medications, and "the median value of undeclared payments from companies marketing 1 of the 10 high-revenue medications recommended in the CPGs was $522 (interquartile range, $0-$40,444) from two companies," the researchers said.

The study findings were limited by several factors including "potential inaccuracies in CMS-OP reporting, which are rarely corrected, and lack of generalizability outside the United States" and by the limited time frame for data collection, which may have led to underestimation of conflicts for the guidelines, the researchers noted. In addition, "we did not have access to guideline voting records and thus did not know when conflicted panel members recommended against a medication or recused themselves from voting," they said.

Mr. Khan disclosed research funding from AbbVie and Ferring Pharmaceuticals.

In a second research letter, half of the authors of gastroenterology guidelines received payments from industry, wrote Tyler Combs, BS, of Oklahoma State University, Tulsa, and his colleagues. Previous studies have reviewed the financial conflicts of interest in specialties including oncology, dermatology, and otolaryngology, but financial conflicts of interest among authors of gastroenterology guidelines have not been examined, the researchers said.

'Our finding that FCOI disclosure only corroborates with OPD payment records between 19% and 34% of the time also suggests that guidance from the ACG may be needed to improve FCOI disclosure efforts in future iterations of gastroenterology CPGs.'

Mr. Combs and his colleagues identified 15 CPGs published by the American College of Gastroenterology between 2014 and 2016. They identified 83 authors, with an average of 4 authors for each guideline. Overall, 53% of the authors received industry payments, according to based on data from the 2014 to 2016 Centers for Medicare & Medicaid Services Open Payments database (OPD).

However, OPD information was not always consistent with information published with the guidelines, the researchers noted. They found that 16 (19%) of the 83 authors both disclosed financial conflicts of interests in the CPGs and had received payments according to OPD or had disclosed no financial conflicts of interest and had received no payments according to OPD. In addition, 49 (34%) of 146 cumulative financial conflicts of interest disclosed in the CPGs and 148 relationships identified on OPD were both disclosed as financial conflicts of interest and evidenced by OPD payment records. In this review, the median total payment was $1,000, with an interquartile range from $0 to $39,938.

The study findings were limited by a relatively short 12-month time frame, the researchers noted. However, "our finding that FCOI [financial conflicts of interest] disclosure only corroborates with OPD payment records between 19% and 34% of the time also suggests that guidance from the ACG [American College of Gastroenterology] may be needed to improve FCOI disclosure efforts in future iterations of gastroenterology CPGs," they said.

The researchers had no financial conflicts to disclose.

ginews@gastro.org

SOURCE: Combs T et al. JAMA Intern Med. 2018 Oct 29. doi: 10.1001/jamainternmed.2018.4730; Khan R et al. JAMA Intern Med. 2018 Oct 29. doi: 10.1001/jamainternmed.2018.5106.

PERSPECTIVE

Statement from the AGA on the integrity of AGA's clinical guideline process

The American Gastroenterological Association (AGA) understands how important it is for AGA members, patients, and the public at large to have access to the most trustworthy, actionable, and evidence-based guidelines in order to achieve the highest possible quality of patient care. In developing guidelines, our goal is to maintain a high level of methodologic rigor through the utilization of an evidence-based approach that is very transparent.

However, not all clinical guidelines are created with equal rigor. Clinicians should examine guidelines closely and consider whether or not they follow the Academy of Medicine's (formerly the Institute of Medicine's) standards for trustworthy clinical guidelines. The guideline should be based on a systematic review of the evidence, focus on transparency, have a rigorous conflict of interest system in place, include the involvement of an unconflicted Grading of Recommendations Assessment, Development and Evaluation (GRADE) system-trained methodologist, ideally as a co-chair, and the recommendations should be concise and actionable. AGA follows a transparent, independent guideline development process that is not subject to company influence or bias and fully complies with the Academy of Medicine's criteria for trustworthy guidelines.

AGA has been proactive in developing policies to minimize bias in our guidelines. AGA requires that the Chair of the Guideline Development Group, and a majority of Guideline (and other clinical practice documents) Development Group members are free of conflicts of interest relevant to the subject matter of the guideline. At the time of invitation, we ask our panel members to disclose any and all potential conflicts. Furthermore, all author disclosures are verified by means of accessing publicly available sources (such as the Centers for Medicare and Medicaid Services' Open Payment database) prior to their involvement on the panel.

AGA strives to be transparent in reporting commercial bias and independent of any industry influence in the development of our clinical practice documents. Our goal is to produce the most trustworthy, actionable, and evidence-based guidelines possible for our members.

Learn more about AGA's clinical guideline process (https://www.gastro.org/guidelines).

Yngve T. Falck-Ytter, MD, AGAF, is chair, and Shahnaz Sultan, MD, MHSc, AGAF, is chair-elect, AGA Institute Clinical Guidelines Committee.

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PRACTICE MANAGEMENT TOOLBOX: Making a case for patient-reported outcomes in clinical inflammatory bowel disease practice

BY ERICA R. COHEN, MD, AND GIL Y. MELMED, MD, AGAF

Patients seek medical care when they perceive a deterioration in their health. Gastroenterologists and health care providers are trained to seek out clinical, laboratory, radiologic, and endoscopic evidence of pathology. Conventional endpoints in inflammatory bowel disease (IBD) clinical trials and clinical care may fail to capture the full health status and disease experience from the patient perspective. The Food and Drug Administration has called for the development of coprimary endpoints in research trials to include an objective measure of inflammation in conjunction with patient-reported outcomes (PROs). The objective is to support labeling claims and improve safety and effectiveness in the drug approval process.[1,2] There is also growing recognition that high-value care includes management of biologic and psychosocial factors to enable patients with chronic diseases to regain their health. Clinicians might follow suit by incorporating valid, reliable PRO measures to usual IBD care in order better to achieve patient-centered care, inform decision making, and improve the care provided.

What are patient-reported outcomes?

The FDA defines a PRO as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." Two PROs are used to measure various aspects of health including physical, emotional, or social domains. PROs have emerged as tools that may foster a better understanding of the patient's condition, which may go beyond disease activity or symptoms. In effect, incorporating PROs into clinical practice enables a model of "coproduction" of health care, and may contribute to a more reciprocal patient-provider interaction where the needs of the patient may be more fully understood and incorporated into decision-making that may lead to improved patient satisfaction and outcomes.[3,4]

There are hundreds of available PROs in gastroenterology,[5] ranging from simple (characterizing pain with a basic numeric rating scale) to complex multidomain, multi-item instruments. PROs may cover symptom assessment, health-related quality of life, and adherence to and satisfaction with treatment, and may be generic or disease specific. Numerous PROs have been developed for patients with IBD. Commonly used PROs in IBD include severity scales for pain, defecatory urgency, and bloody stool, and several disease-specific and generic instruments assessing different health-related quality-of-life domains have been used in research studies for patients with IBD.

The current approach to patient-centered care for IBD is limited

IBD is a difficult disease to manage – in part because there is no known biomarker that accurately reflects the full spectrum of disease activity. Numerous indices have been developed to better quantify disease activity and measure response to treatment. Among the most frequently used indices in clinical trials are the Crohn's Disease Activity Index (CDAI) and (for ulcerative colitis [UC]) the Mayo Clinic Score. These endpoints incorporate signs and symptoms, laboratory findings (in the CDAI), and endoscopic assessments. The CDAI is a suboptimal instrument because of a lack of correlation with endoscopic inflammation and potential confounding with concomitant gastrointestinal illnesses, such as irritable bowel syndrome.[6] The Mayo Clinic Score is difficult to interpret because of some subjective elements (what is considered a normal number of stools per day?); vagueness (mostly bloody stools more than half the time?); and need for a physician assessment, which often does not correspond with the patient's perception of their disease.[7] From a research perspective, this disconnect can compromise the quality of trial data. Clinically, it can negatively impact patients' satisfaction and impair the patient-provider relationship.[8]

To that end, regulatory agencies, scientific bodies, and health care payors are shifting toward a more "patient-centered" approach with an emphasis on PROs. However, although the FDA is incorporating the patient perspective in its trials, measuring meaningful outcomes in day-to-day clinical care is challenging. In the absence of active inflammation, more than 30% of patients with IBD still suffer from gastrointestinal symptoms.[9] Furthermore, physicians frequently underestimate the effect of depression, anxiety, fatigue, and sleep on patient health. Likewise, some patients with active small-bowel Crohn's disease (CD) may experience few gastrointestinal symptoms but have profound fatigue, weight loss, and impaired quality of life. A focused assessment for disease activity may fail to identify aspects of health most relevant or important to individual patient well-being. There is a need for effective, efficient, and standardized strategies to better understand the concerns of the individual seeking help.

DR. COHEN

DR. MELMED

Although there are several PROs that measure disease activity primarily for clinical research trials,[10] their prevalence in gastroenterology practices has not been assessed. Most likely, few clinical practices currently integrate standardized PROs in routine patient care. This may be because of several reasons, including lack of awareness of newly developed PROs, administrative burden including time and resources to collect PROs, potentially complex interpretation of results, and perhaps a reluctance among physicians to alter traditional patient interview methods of obtaining information about the health status of their patients. For effective use in clinical care, PROs require simple and relevant interpretation to add value to the clinician's practice, and must minimally impact clinical flow and resources. The use of Internet-enabled tablets has been shown to be a feasible, efficient, and effective

Continued on following page

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Continued from previous page

means of PRO assessment in gastroenterology practices, with good levels of patient satisfaction.[11]

Reaping potential benefits of patient-reported outcomes

The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) is an initiative developed to investigate and promote implementation of PRO measures among patients with chronic diseases. The collection of PROMIS measures has been shown to be feasible at a tertiary care IBD center, enabling a biopsychosocial model of care.[12] Likewise, implementation of PROs in other clinical areas including oncology, orthopedics, and rheumatology has been robust.

In an innovative orthopedic study, PROMIS measures collected and linked to the electronic medical record predicted the likelihood of a clinically meaningful benefit from foot and ankle surgery.[13] This facilitated tailored patient-specific preoperative discussions about the expected benefit of surgery. In a study at a rheumatology clinic patients with rheumatoid arthritis were asked to identify their highest priority treatment targets using PROMIS domains (fatigue, pain, depression, social function). The highest priority domain was tracked over time as a patient-centered marker of health, essentially personalizing measures of success for the individual patient.[14]

PROs have the unique potential to affect multiple levels of health care. At the patient level, PRO data can identify specific concerns, manage expectations of recovery, and tailor treatment decisions to personal preference. At the population level, PRO data can be used to standardize aspects of care to understand comparative health and disease among all patients in a practice or relative to outside practices, identify outliers, and drive improvement.

Optimizing PROs for use in clinical trials: CD–PROs and UC–PROs

Developing standardized, validated instruments according to FDA guidance is a complex process. The lack of an FDA-approved PRO has resulted in substantial variability in the definitions of clinical response or remission in clinical trials to date.[15] As a result, IBD-specific PROs (CD-PRO and UC-PRO) are being developed under FDA guidance for use in clinical trials.[16] With achievement of prequalification for open use, UC-PRO and CD-PRO will cover five IBD-specific outcomes domains or modules: 1) bowel signs and symptoms, 2) systemic symptoms, 3) emotional impact, 4) coping behaviors, and 5) IBD impact on daily life. The bowel signs and symptoms module may also incorporate a functional impact assessment. Each module includes numerous pertinent items (e.g., "I feel worried," "I feel scared," "I feel alone" in the emotional impact module) and are currently being tailored and scored for practicality and relevance. It is hoped that UC-PRO and CD-PRO in final form will be relevant and applicable for clinical trials and gastroenterology practices alike.

Because the development of the UC-PRO and the CD-PRO is still underway, interim PROs are being used in ongoing clinical trials. These interim measures were extracted from existing components of the CDAI, Mayo Clinic Score, and UC Disease Activity Index. The CD PRO-2 consists of two items: abdominal pain and stool frequency. The UC PRO-2 is composed of rectal bleeding and stool frequency. The PRO-3 adds an item regarding general well-being. The sensitivity of these PROs was tested in studies for CD and UC. Both PROs performed similarly to their respective parent instrument. Important limitations include the lack of validation, and the fact that these interim measures were derived from parent measures with acknowledged limitations as previously discussed. Current clinical trials are coupling these interim measures with endoscopic data as coprimary endpoints.

PROs in routine clinical practice: Are we ready for prime time?

Few instruments developed to date

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Table 1. General and IBD-specific patient-reported outcomes

Domain	Instrument	Comments	Items, n
Overall well-being	Inflammatory Bowel Disease Questionnaire[17]	Quality of life (QOL): bowel, systemic, social, emotional	32
	Inflammatory Bowel Disease QOL[18]		36
	Inflammatory Bowel Disease Questionnaire-short form[19]		10
	Cleveland Global QOL Score[20]	QOL after pouch surgery	3
Disability	IBD-Disability Index[21]	Pain, body image, education and work, emotions, energy, interpersonal, joint pain, defecation, sexual function, sleep	28
	IBD-Disk (Shorted Disability Index)[22]	Disk has visual representation	10
Disease activity	PRO2[23]	Brief	2
		Interim use in clinical trials	10
	Simple Clinical Colitis Activity Index[24]	Initial colitis diagnosis and relapse	
Pain	IBD-Control Questionnaire[25]	Physical symptoms, social and emotional functioning, treatment, and disease control perceptions	13
	Visual analog scale	Pain intensity	1
	Numeric rating scale	Pain intensity	1
Depression and anxiety	Brief Pain Inventory[26]	Identifies pain location on body diagram	11
	Patient Health Questionnaire-9[27]		9
	Hospital Anxiety and Depression Scale[28]	Used in outpatient and inpatient settings	14
		Requires access to use free of purchase	7
	Generalized Anxiety Disorder-7[29]		
Work and productivity	Work Productivity and Activity Impairment: Crohn's Disease[30]	Absenteeism, degree of reduced productivity caused by IBD	6
Fatigue	Multidimensional Fatigue Inventory[31]	General, physical, and mental fatigue; reduced activity and motivation	20
	IBD-Fatigue Scale[32]	Severity and frequency of fatigue, impact on life	30
Miscellaneous	Rating Form of Patient Concerns[33]	Disease activity, body stigma, sexual intimacy, interpersonal relationships	25
	Perceived Stress Scale[34]	Related to objective events and effectiveness of stress reduction interventions	10

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have been widely implemented into routine IBD clinical practice. Table 1 highlights commonly available or recently developed PROs for IBD care. As clinicians strive to more effectively integrate PROs into clinical practice, we propose a three-step process to getting started: 1) select and administer a PRO instrument, 2) identify areas of impairment and create a targeted treatment strategy to focus on those areas, and 3) repeat the same PRO at follow-up to assess for improvement. The instrument can be administered before the visit or in the clinic waiting room. Focus a portion of the patient's visit on discussing the results and identifying one or more domains to target for improvement. For example, the patient may indicate diarrhea as his/her most important area to target, triggering a symptom-specific investigation and therapeutic approach. The PRO may also highlight social or emotional impairment that may require an ancillary referral. The benefits of this PRO-driven approach to IBD care are twofold. First, the patient's primary concerns are positioned at the forefront of the clinical visit. Second, aligning the clinician's focus with the patient input may actually help to streamline each visit and improve overall visit efficiency and patient satisfaction.

The following are novel, potentially useful measures to consider for clinical use. The 13-item IBD-Control Questionnaire provides a rapid and user-friendly assessment of disease control from the patient's perspective.[25] Capturing physical symptoms and social function, it includes a visual analog scale of perceived disease control. It is practical and may identify patients in a quiescent state. This is for clinicians looking to home in on individual concerns or triage the urgency of a follow-up appointment. The IBD Disk is a shortened visual adaptation of the validated IBD-Disability Index.[22] Patients score their level of agreement with statements regarding pain, defecation, social interactions, education, work, sleep, energy, emotions, body image, sexual function, and joint pain over the previous week. The visual feedback allows patients and physicians to see changes in disease burden over time, highlight areas of persistent impairment, and try to improve medication adherence. This may be useful for practices with few readily available ancillary services, such as a social worker or dedicated IBD nurse.

Take-away points

1. Conventional endpoints in clinical trials and clinical care often fail to capture the full health status from the patient perspective.
2. The development of validated patient-reported outcomes to be used as coprimary endpoints in clinical trials is underway. However, this has yet to be adapted into clinical care.
3. This article provides examples of general and IBD-specific PROs along with a proposed process for streamlining them into a busy clinical practice.
4. Using PROs in clinical practice has the potential to improve the quality and value of care delivered by addressing and monitoring the many facets of living with inflammatory bowel disease.

Conclusions

As therapies for IBD improve, so should standards of patient-centered care. Clinicians must actively seek and then listen to the concerns of patients and be able to address the multiple facets of living with a chronic disease. PROs empower patients, helping them identify important topics for discussion at the clinical visit. This affords clinicians a better understanding of primary patient concerns before the visit, and potentially improves the quality and value of care. At first, the process of incorporating PROs into a busy clinical practice may be challenging, but targeted treatment plans have the potential to foster a better patient – and physician – experience.

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Dr. Cohen is in the division of digestive and liver diseases; Dr. Melmed is director, clinical inflammatory bowel disease, director, clinical research in the division of gastroenterology, and director, advanced inflammatory bowel disease fellowship program, Cedars-Sinai Medical Center, Los Angeles. Dr. Melmed is a consultant for AbbVie, Boehringer Ingelheim, Celgene, Genentech, Janssen, Pfizer, Samsung Bioepis, Takeda, and UCB; and received support for research from Prometheus Labs. The remaining author discloses no conflicts.

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