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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

MARCO SANCHEZ/UCSF DOCUMENTS & MEDIA

Dr. Uma Mahadevan, with a group of organizations interested in obstetric and IBD care, published a much-need care plan for pregnant IBD patients.

AGA publishes care pathway for IBD in pregnancy

BY AMY KARON
MDedge News

Ideally, pregnant women with inflammatory bowel disease (IBD) should receive coordinated care from gastroenterologists and maternal-fetal medicine specialists, plus additional input from nutritionists, lactation counselors, and colorectal surgeons as needed, states a new report from the American Gastroenterological Association.

But in reality, these women often receive scant and conflicting advice from health care providers, writes Uma Mahadevan, MD, AGAF, of the University of California, San Francisco, with her associates in Gastroenterology.

An "explosion" of new treatments in the past 15 years has given hope to many women with IBD who wish to be healthy enough to conceive, the experts noted. But in a recent AGA survey, more than 40% of obstetrician/gynecologist (OB/GYN) providers felt that women with IBD received inadequate information about pregnancy, compared with patients with other immune-mediated diseases. Strikingly, 94% of surveyed clinicians said they had patients stop taking their IBD

See **IBD care** · *page 20*

DAAs reduce mortality, cancer risk in HCV study

Large study with significant results.

BY ANDREW D. BOWSER
MDedge News

Direct-acting antivirals significantly decrease risk of hepatocellular carcinoma and mortality in persons with hepatitis C, according to results of the first prospective, longitudinal study to evaluate the effect of the drugs on complications related to the infection.

Compared with no treatment, DAA therapy cut risk of hepatocellular carcinoma by about one-third and all-cause mortality by about half in the study, which included about 10,000 adult patients with chronic hepatitis C virus (HCV) infection treated at 1 of 32 hepatology centers in France (NCT01953458).

There were no signs of increased risk of hepatocellular carcinoma during treatment with DAAs, providing more evidence refuting earlier, single-center reports that had suggested an increased incidence early after treatment. These findings also counterbalance a recent Cochrane review that could not confirm or reject a potential benefit of drugs on long-term morbidity and mortality.

Results of the study, published in the Lancet, are based on analysis of 9,895 patients, including 7,344 who started

See **DAAs** · *page 23*

INSIDE

Distinct features found in young-onset CRC

BY ANDREW D. BOWSER
MDedge News

Young-onset colorectal cancer (CRC) has distinct clinical and molecular features, compared with disease diagnosed later in life, according to investigators who conducted a review that included more than 36,000 patients.

CRC patients younger than 50 years of age were more likely to have distal primary tumors, synchronous metastatic disease, and microsatellite instability (MSI) than were older patients, investigators said. Conversely, those younger patients were less likely to have BRAF V600 mutations than were patients 50 years old and older, the investigators reported in the journal Cancer.

Very young patients were more likely to have signet-

See **Distinct** · *page 22*

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LETTER FROM THE EDITOR: More cost compression coming


DR. ALLEN

In mid-March, the President released his FY2020 budget proposal. Traditionally, the White House budget has little relation to the ultimate budget since Congress actually creates the final iteration (assuming the government can pass a budget at all). This budget cuts funding for the NIH, Medicare, Medicaid, and most agencies not related to defense, border security, or the TSA. No matter what the final version looks like, the federal deficit will balloon as a result of last year's tax cuts that were combined with relentless increases in entitlement program spending. The message for health care leaders is clear; Since we are responsible for an enormous percentage of committed federal and state spending, we will be in the cross-hairs of cost compression.

As we enter the 2020 election cycle in earnest, politicians will argue about "Medicare for All" versus government overreach. We will wrestle with competing philosophies of States' Rights versus Federalism. As physicians, we must advocate for a system of funds flow and regulatory power that we believe best serves our patients within a financially sustainable framework.

On to this month's issue – there are two stories on early-age colon cancer. A page one story adds to our understanding of the molecular pathways involved (microsatellite instability) and tumor location. Another story points out that younger CRC patients often go undiagnosed or are misdiagnosed. The AGA has published important clinical guidance about pregnancy and IBD and switching from biologic medications to biosimilars. Finally, an enormously important study, published in The Lancet, confirmed that hepatitis C treatment with direct-acting antiviral medications reduces mortality and cancer risk – something we suspected but needed confirmed.

I hope to see everyone at DDW next month.

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

DDSEP eight
Digestive Diseases Self-Education Program

Quick Quiz

Q1. A 31-year-old G2P1 woman presents to your clinic for pregnancy counseling. She is currently 12 weeks pregnant, and states that her first pregnancy was complicated by intrahepatic cholestasis of pregnancy (ICP) development at 29 weeks. She developed severe pruritus, and the baby was delivered prematurely. She is concerned about complications with her current pregnancy and is wondering about therapy if ICP recurred at the same point in her pregnancy.

Which of the following is correct regarding the management of ICP in this patient?

A. The only therapy for ICP is delivery of the baby with symptom onset
B. Her risk of recurrent ICP is the as the general population
C. If she develops ICP, recommend therapy with ursodeoxycholic acid
D. If she develops ICP, recommend therapy with cholestyramine
E. If she develops ICP, recommend therapy with hydroxyzine

Q2. A 47-year-old man with a history of chronic diarrhea presents with black, tarry stools for 2 days. Laboratory evaluation shows hemoglobin 8.9 g/dL (normal: 14-17 g/dL), platelet 201 x 10^3/mcL (normal: 150-350 mcL), blood urea nitrogen 40 mg/dL (normal: 8-20 mg/dL), creatinine 0.8 mg/dL (normal: 0.7-1.3 mg/dL), and calcium 12.5 mg/dL (normal: 9-10.5 mg/dL). An upper endoscopy reveals LA grade C esophagitis and a 1-cm clean-based ulcer in the duodenal bulb. Gastric biopsies show no *H. pylori* on H&E stain. He denies any history of NSAID or aspirin use.

What would be the most appropriate next step in management?

A. Repeat upper endoscopy in 6 weeks
B. Transfuse 1 unit packed red blood cells
C. Obtain fasting serum gastrin level
D. Sucralfate slurry four times daily

The answers are on page 20.

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FROM THE AGA JOURNALS

High-calorie diet may worsen Wilson disease

BY WILL PASS
MDedge News

A high-calorie diet may cause earlier onset of more severe Wilson disease, according to a rodent study.

If translatable to humans, the results could explain "striking phenotype-genotype discrepancies" between patients with Wilson disease, and may give reason to monitor nutrition more closely, particularly dietary levels of fat and sugar, reported lead author Claudia Einer, a PhD candidate at the German Research Center for Environmental Health in Neuherberg, Germany, and her colleagues. Their findings clarify an association between impaired copper metabolism, which defines Wilson disease, and liver steatosis, a common finding in affected patients.

"Indeed, Wilson disease often may be misdiagnosed as nonalcoholic fatty liver disease (NAFLD)," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology. They noted that previous reports showed similar mitochondrial alterations in the livers of patients with NAFLD and those with Wilson disease. Furthermore, in a case report of two twins with Wilson disease, the twin with bulimia nervosa developed severe liver disease, whereas the other twin, who was undernourished, had mild liver disease. Considering these observations and other supportive evidence, the investigators tested this apparent relationship between a high-fat diet and liver damage in Wilson disease.

"The rationale of this study was that both enriched copper and fatty acids cause bioenergetic defects and therefore synergistically and detrimentally may coincide on hepatic mitochondria, which was found to be dramatically the case," the investigators wrote.

The study involved homozygous Atp7b−/− rats, which mirror Wilson disease, and heterozygous Atp7b+/− rats, which served as control subjects because they lack copper accumulation. The high-calorie diet contained high fat and sugar levels to mirror "the eating habits in Western society, causing the 'American-lifestyle-induced-obesity syndrome.' "

Within several weeks of starting the high-calorie diet, both control and Wilson disease rats showed higher liver triglyceride levels and visceral fat mass compared with rats on the normal diet, with liver histology also showing macrosteatosis and increased NAFLD Activity Score (NAS). Control rats maintained similar body and liver weights regardless of diet; in contrast, Wilson disease rats on the high-calorie diet showed increased liver weight, compared with Wilson disease rats on the normal diet. In addition, Wilson disease rats fed the high-calorie diet had clinical liver injury, supported by elevated aspartate aminotransferase levels and gross hepatic damage. Under the microscope, histology revealed widespread necrosis, apoptosis, inflammation, and fibrosis; findings were sufficient to constitute nonalcoholic steatohepatitis in all Wilson disease rats fed the high-calorie diet, compared with just one-third of the control rats receiving high calories. Additional testing showed that Wilson disease rats fed the high-calorie diet had disease onset 20 days sooner than did Wilson disease rats fed the normal diet.

"This is a remarkable disease acceleration," the investigators noted, highlighting the median survival of 106 days in Wilson disease rats fed a normal diet.

Copper testing showed that Wilson disease rats fed the high-calorie diet had high serum levels of non–ceruloplasmin-bound copper, which is a sign of overt liver damage; based on histologic findings, the copper likely came from destroyed hepatocytes. Regardless of diet type, Wilson disease rats developed high levels of copper within the liver, suggesting comparable copper consumption via water sources. Regardless of genotype, the high-calorie diet led to higher mitochondrial copper levels than those of the normal diet, but Wilson disease rats showed the highest levels of copper sequestration in mitochondria, to an extreme degree.

"Importantly," the investigators wrote, "such increased mitochondrial copper significantly correlated with a higher NAS and a progressive Histologic Activity Index score."

Closer inspection showed that the mitochondria of Wilson disease rats were abnormal regardless of diet, but those fed the high-calorie diet had "a most severe mitochondrial phenotype," including detached membranes and ballooned cristae.

"These structural impairments were paralleled by remarkable mitochondrial functional deficits," the investigators reported, referring to a significant decrease in adenosine triphosphate production and an increase in mitochondrial H_2O_2. In response to these mitochondrial abnormalities, cholesterol-related enzymes quadrupled, most prominently for biliary excretion. The investigators summed up these hepatic events as a "toxic triad of adenosine triphosphate depletion, increased reactive oxygen species, and increased bile salts [that led] to an earlier onset of the disease and to enhanced disease progression."

To complete the set of experiments, researchers gave rats the copper chelator methanobactin. This treatment effectively mitigated structural and functional abnormalities in mitochondria, which drove serum levels of AST, copper, and bile salts toward normalcy. Although treatment halted overt liver damage, histology revealed that resolution was incomplete.

"We conclude that lipid accumulation in copper-burdened hepatocytes may represent a 'second-hit' in Wilson disease, inducing liver damage, and suggest that further research should establish whether dietary counseling of Wilson disease patients may be of therapeutic benefit," the investigators concluded.

The study was funded by Deutsche Forschungsgemeinschaft and the WiFoMed Society. The investigators reported no conflicts of interest.

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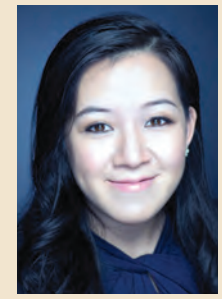
SOURCE: Einer C et al. Cell Mol Gastroenterol Hepatol. 2019 Jan 11. doi: 10.1016/j.jcmgh.2018.12.005.

Steatosis is a hallmark of fatty liver disease and is present in liver cells in the early phase of copper-induced injury in Wilson disease (WD). Early on in WD, hepatocellular mitochondria develop swollen cristae and dense deposits that improve with treatment of the copper overload. Ms. Einer and colleagues demonstrated that administration of a high-calorie diet to a rodent model of WD accelerated mitochondrial and hepatocellular injury, causing earlier-onset liver disease. Copper was the "accelerant" of injury because of its toxic effects on hepatic mitochondria. The investigators used a novel metal chelator, Methanobactin, derived from a proteobacterium *Methylosinus trichosporium*, to rescue mitochondria from copper-induced damage, showing that copper is primary to the process.


DR. SCHILSKY


DR. TO

These investigations suggest that "decoppering" patients may be critical to prevent the secondary injury due to fatty liver caused by diet. This should raise alarm bells for clinicians treating WD patients as, not only may we need to increase our emphasis on "decoppering" the liver, but we should consider intensive dietary counseling to prevent fatty change because of diet. The wide range of phenotype in WD is due to many factors, and we can now add dietary intake of fructose and fat as yet one more potential influence. Clearly well beyond the effect of the specific ATP7B gene mutations responsible for WD, environmental and extragenic effects may dominate the determination of our patients' WD phenotype. In understanding the basic mechanisms for some of these factors, such as diet, perhaps we may influence the natural history of our WD patients' disease more favorably.

Michael L. Schilsky, MD, and Uyen Kim To, MD, are members of the Center of Excellence for Wilson Disease at Yale University, New Haven. Conn. Dr. Schilsky and Dr. To are investigators in the sponsored trials of WTX101 by Wilson therapeutics (now Alexion) and TETA4 by GMPO. Dr. Schilsky is adviser to Alexion, GMPO, and Vivet Therapeutics.

FROM THE AGA JOURNALS

One-time, universal hepatitis C testing cost effective, researchers say

BY AMY KARON
MDedge News

Universal one-time screening for hepatitis C virus infection is cost effective, compared with birth cohort screening alone, according to the results of a study published in Clinical Gastroenterology and Hepatology.

The Centers for Disease Control and Prevention and the U.S. Preventive Services Task Force recommend testing all individuals born between 1945 and 1965 in addition to injection drug users and other high-risk individuals. But so-called birth cohort screening does not reflect the recent spike in hepatitis C virus (HCV) cases among younger persons in the United States, nor the current recommendation to treat nearly all chronic HCV cases, wrote Mark H. Eckman, MD, of the University of Cincinnati, and his associates.

Using a computer program called Decision Maker, they modeled the cost-effectiveness of universal one-time testing, birth cohort screening, and no screening based on quality-adjusted life-years (QALYS) and 2017 U.S. dollars. They assumed that all HCV-infected patients were treatment naive, treatment eligible, and asymptomatic (for example, had no decompensated cirrhosis). They used efficacy data from the ASTRAL trials of sofosbuvir-velpatasvir as well as the ENDURANCE, SURVEYOR, and EXPEDITION trials of glecaprevir-pibrentasvir. In the model, patients who did not achieve a sustained viral response to treatment went on to complete a 12-week triple direct-acting antiviral (DAA) regimen (sofosbuvir, velpatasvir, and voxilaprevir).

Such findings have spurred experts to revisit guidelines on HCV screening, but universal testing is controversial when some states, counties, and communities have a low HCV prevalence.

Based on these assumptions, universal one-time screening and treatment of infected individuals cost less than $50,000 per QALY gained, making it highly cost effective, compared with no screening, the investigators wrote. Universal screening also was highly cost effective when compared with birth cohort screening, costing $11,378 for each QALY gained.

"Analyses performed during the era of first-generation DAAs and interferon-based treatment regimens found birth-cohort screening to be 'cost effective,' " the researchers wrote. "However, the availability of a new generation of highly effective, non–interferon-based oral regimens, with fewer side effects and shorter treatment courses, has altered the dynamic around the question of screening." They pointed to another recent study in which universal one-time HCV testing was more cost effective than birth cohort screening.

Such findings have spurred experts to revisit guidelines on HCV screening, but universal testing is controversial when some states, counties, and communities have a low HCV prevalence. In the model, universal one-time HCV screening was cost effective (less than $50,000 per QALY gained), compared with birth cohort screening as long as prevalence exceeded 0.07% among adults not born between 1945 and 1965. The current prevalence estimate in this group is 0.29%, which is probably low because it does not account for the rising incidence among younger adults, the researchers wrote. In an ideal world, all clinics and hospitals would implement an HCV testing program, but in the real world of scarce resources, "data regarding the cost-effectiveness threshold can guide local policy decisions by directing testing services to settings in which they generate sufficient benefit for the cost."

Partial funding came from the National Foundation for the Centers for Disease Control and Prevention (CDC Foundation), with funding provided through multiple donors to the CDC Foundation's Viral Hepatitis Action Coalition. Dr. Eckman reported grant support from Merck and one coinvestigator reported ties to AbbVie, Gilead, Merck, and several other pharmaceutical companies.

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SOURCE: Eckman MH et al. Clin Gastroenterol Hepatol. 2018 Sep 7. doi: 10.1016/j.cgh.2018.08.080.

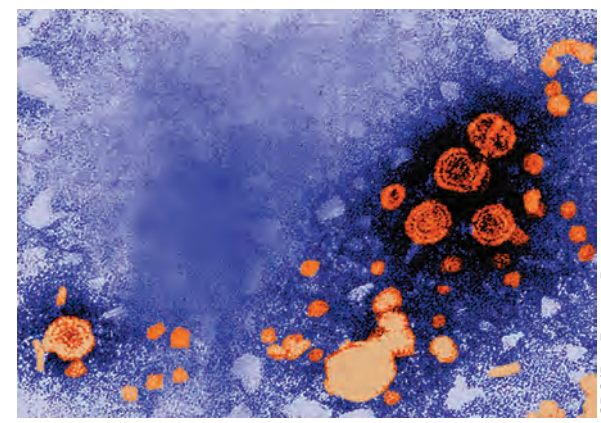
Novel capsid assembly modulator promising in HBV

BY AMY KARON
MDedge News

For adults with chronic hepatitis B virus infection, treatment with a novel investigational capsid assembly modulator was well tolerated and showed antiviral activity against HBV, according to the results of a phase 1 study of 73 patients.

"Substantial and correlated reductions in serum HBV DNA and HBV RNA levels were observed consistently with the higher-dose cohorts and were notably greatest for combination treatment with NVR 3-778 and pegIFN [pegylated interferon]," Man Fung Yuen, MD, of the University of Hong Kong, and his associates wrote in a report published in Gastroenterology. Hence, this first-in-class capsid assembly modulator might help prolong treatment responses, "most likely as a component of new combination treatment regimens for HBV-infected patients." However, one patient developed severe rash immediately after completing treatment that took 6 months of intensive outpatient treatment to resolve, they noted.

Chronic viral hepatitis due to HBV is a major cause of early death worldwide, and new therapies are needed to help prevent severe liver disease and liver death from this infection. Current treatments for HBV infection consist of nucleoside or nucleotide analogs or pegylated interferon. These suppress HBV replication in many patients, but most patients do not achieve durable responses. Consequently, most patients require long-term treatment with HBV nucleosides and nucleotide analogs, which they may find difficult to tolerate or adhere to and to which their infections can become resistant, the researchers said.



CDC/Dr. Erskine Palmer

The HBV virion contains a viral core protein (HBc) that is required to encapsidate viral polymerase and pregenomic HBV RNA into a nucleocapsid. To target this process, researchers developed NVR 3-778, a first-in-class, orally bioavailable small molecule that binds HBc so that HBc forms a defective capsid that lacks nuclear material. Hence, NVR 3-778 is intended to stop the production of HBV nucleocapsids and keep infected cells from releasing the enveloped infectious viral particles that perpetuate HBV infection.

To assess the safety, pharmacokinetics, and antiviral activity of NVR 3-778, the researchers conducted a phase 1 study of 73 patients with chronic HBV infection who tested positive for hepatitis B e-antigen (HBeAg) and had no detectable cirrhosis. Patients were randomly assigned to receive oral NVR 3-778

Continued on following page

FROM THE AGA JOURNALS

Continued from previous page

(100 mg, 200 mg, or 400 mg daily or 600 mg or 1,000 mg twice daily) or placebo for 28 days. Some patients received combination therapy with pegylated interferon plus either NVR 3-778 (600 mg twice daily) or placebo. Treatment was generally well tolerated, and adverse events were usually mild and deemed unrelated to therapy. No patient stopped treatment for adverse effects.

The only serious adverse event in the study consisted of grade 3 rash that developed in a 42-year-old male after 22 days of treatment at the lowest dose of NVR 3-778 (100 mg per day). This patient completed treatment and ultimately developed a severe papulovesicular rash with a predominantly acral distribution over the hands, arm, side of neck, and one leg (palmar plantar erythrodysesthesia), the researchers said. "There were no perioral or mucosal lesions, no ecchymotic skin involvement, no bullae, and no systemic manifestations or hematological abnormalities," they wrote. "The rash was subsequently managed with a psoriasis-like treatment regimen of psoralen, ultraviolet light, and topical steroid ointment during outpatient follow-up and resolved after approximately 6 months."

Another three cases of "minor" skin rash were considered probably related to treatment in the cohort that received 600 mg NVR 3-778 b.i.d. plus pegylated interferon, the investigators said. Two additional cases of mild rash were deemed unrelated to treatment.

Chronic viral hepatitis due to HBV is a major cause of early death worldwide, and new therapies are needed to help prevent severe liver disease and liver death from this infection.

"The observed reductions in HBV RNA confirmed the novel mechanism of NVR 3-778," the researchers concluded. "This class of compounds can also inhibit replenishment of intranuclear covalently closed circular DNA over time and may have immunomodulatory properties." Longer treatment periods would be needed to study these mechanisms and to quantify reductions in serum HBsAg and HBeAG, they noted.

Novira Therapeutics developed NVR 3-778 and is a Janssen Pharmaceutical Company. Janssen provided funding for editorial support. Dr. Yuen disclosed relationships with AbbVie, Biocartis, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Ionis, Roche, Vir Biotechnology, and several other pharmaceutical companies. Other coinvestigators disclosed ties to pharmaceutical companies; eight reported employment by Novira or a Janssen company.

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SOURCE: Yuen MF et al. Gastroenterology. 2019 Jan 5. doi: 10.1053/j.gastro.2018.12.023.

FROM THE AGA JOURNALS

Interactive online module improved detection of Barrett's

BY AMY KARON
MDedge News

An online educational tool for endoscopists helped improve their detection of Barrett's esophagus–related neoplasia (BORN), researchers reported in the April issue of Gastroenterology.

In tests administered before and after training, endoscopists increased their rates of BORN detection by a median of 30% (*P* less than .001), reported J.J. Bergman, MD, PhD, of the University of Amsterdam, together with his associates. "To our knowledge, this is the first validated online, interactive endoscopic training program in our field," they wrote. "Widespread use of this tool might improve management of Barrett's esophagus by general endoscopists."

To develop the program, the investigators recorded high-definition videos of upper endoscopies of patients with either BORN or nondysplastic Barrett's esophagus. They sent these videos to three experts, who used special tools to superimpose their delineations of lesions.

Next, 68 general endoscopists (fellows, early-career general gastroenterologists, and senior general gastroenterologists) watched four batches of 20 videos each. The researchers compared the assessors' interpretations with the experts' to identify the 25 videos with the most educational impact. These were then shown in four batches of five to 121 new assessors (five videos were reserved for pre- and post testing).

From the first to the fourth batch of training videos, assessors sequentially improved their scores for detection, delineation, agreement delineation, and relative delineation of BORN, the researchers said. Among the 121 assessors in the second phase of development, median rates of detection of BORN rose by 30% after training. Furthermore, from baseline to the end of the study, scores rose by 46% for detection, 129% for delineation, 105% for agreement delineation, and 106% for relative delineation (all *P* less than .001). These improvements did not depend on the country of origin of the assessors or their level of endoscopic experience.

This module requires the use of high-definition videos whose resolution is not lost during replay or when viewed on the web, the researchers emphasized. They noted that the module is active, not passive – learners select the video frame to position a biopsy mark and delineate the lesion, and the software then gives them tailored feedback on their choice. Learners also can add and remove the experts' delineations as well as their own during feedback sessions at the end of each batch of videos. This enables them to "fully appreciate the subtle appearance of the lesion on the selected time frame," the investigators wrote.

By completing the training module, "general endoscopists with a wide range of experience and from different countries of origin can substantially and conveniently increase their skills for detection and delineation of early BORN lesions," they concluded. "Therefore, the module could provide training in an essential upper gastrointestinal endoscopic skill that is not otherwise readily available."

The investigators disclosed no external funding sources. They reported having no conflicts of interest.

ginews@gastro.org

SOURCE: Bergman JJ et al. Gastroenterology. 2019 Jan 2. doi: 10.1053/j.gastro.2018.12.021.

Endoscopic mucosal resection and ablation strategies offer the potential for minimally invasive, curative treatment for patients with Barrett's esophagus–associated intramucosal neoplasia. For the gastroenterologist interested in endoscopic prevention and management of esophageal cancer, however, achieving proficiency in performance of these endoscopic techniques represents only part of the requisite preparatory experience. Acquisition of cognitive skills in lesion recognition is a fundamental and underappreciated component to a successful endoscopic treatment paradigm.


DR. YACHIMSKI

This study by Dr. Bergman and colleagues describes development and validation of a high-definition white light endoscopy–based video training module for detection of Barrett's esophagus–related neoplasia. Intensive effort was invested in design of this educational module, which has explicitly set high stakes by carefully selecting "early, endoscopically curable neoplastic lesion[s]" for inclusion – in other words, the failure of an endoscopist to recognize such a lesion and triage the lesion to timely therapy could have profound consequences should disease progress beyond an endoscopically curable stage.

General endoscopist assessors were grouped into three groups based on level of experience. Following completion of the training module, scores in lesion detection and delineation increased irrespective of level of endoscopist experience.

The module is free, CME-accredited, and available for online use. Any endoscopist who performs Barrett's screening, surveillance, and therapy should be motivated and incentivized to engage with this important educational tool.

Patrick Yachimski, MD, MPH, AGAF, is associate professor of medicine, director of pancreatobiliary endoscopy, division of gastroenterology, hepatology & nutrition, Vanderbilt University Medical Center, Nashville, Tenn. He has no conflicts.

Barrett's esophagus uncommon in patients with uncomplicated GERD

BY AMY KARON
MDedge News

Uncomplicated gastroesophageal reflux disease (GERD) accounted for 13.5% of esophagogastroduodenoscopies, but 5.6% of these patients had suspected Barrett's esophagus and only 1.4% had suspected long-segment Barrett's esophagus, researchers reported. The study appears in the April issue of Clinical Gastroenterology and Hepatology.

"The prevalence of suspected Barrett's esophagus is lower than in prior time periods. This raises questions about the utility of esophagogastroduodenoscopies to detect Barrett's esophagus in patients with uncomplicated GERD," wrote Emery C. Lin, MD, of Oregon Health & Science University, Portland, and his associates there and at Massachusetts General Hospital, Boston.

Symptoms of GERD affect more than one in four U.S. adults and are a risk factor for Barrett's esophagus. However, the prevalence of Barrett's esophagus is unclear in patients with dysphagia and in the era of proton pump inhibitors, the researchers said. The American Gastroenterological Association strongly discourages reflexively screening patients with GERD for Barrett's esophagus, but "weakly recommends" screening GERD patients with multiple risk factors for Barrett's esophagus, including chronic GERD, hiatal hernia, older age (50 years and up), white race, male sex, increased body mass index, and intra-abdominal adiposity.

To understand the prevalence and findings of esophagogastroduodenoscopy in patients with GERD without alarm symptoms (including weight loss, dysphagia, and bleeding), the investigators studied 543,103 of these procedures performed at 82 sites in the United States between 2003 and 2013. The data came from the National Endoscopic Database, which generates endoscopy reports using a structured computer form.

A total of 73,535 esophagogastroduodenoscopies (13.5%) were performed for GERD without alarm symptoms. Among these patients, 4,122 (5.6%) had suspected Barrett's esophagus, of which 24.2% had suspected long-segment Barrett's esophagus (3 cm or longer). Among pa-

Continued on page 14

FROM THE AGA JOURNALS

Continued from page 9

tients with uncomplicated GERD, the prevalence of suspected Barrett's esophagus was 5.6%, and the prevalence of long-segment disease was 1.4%.

Although male sex, older age, and white race were significant risk factors for suspected Barrett's esophagus and suspected long-segment disease, 23.6% of esophagogastroduodenoscopies were performed in white men older than 50 years. "We find that low-risk populations with uncomplicated GERD make up a significant number of esophagogastroduodenoscopies done for uncomplicated GERD," the investigators wrote. "If esophagogastroduodenoscopies were limited to patients that met the AGA criteria of being male, white, and age over 50, we would have detected 34 of 47 (72.3%) of esophageal tumors and found suspected Barrett's esophagus in nearly 10%, while reducing the burden of endoscopy by more than 75%."

Hiatal hernia was a significant correlate of suspected Barrett's esophagus (odds ratio, 1.6), the researchers noted. Esophagitis was not associated with suspected Barrett's esophagus overall but did correlate with long-segment disease. Esophagitis might mask underlying short-segment Barrett's esophagus, and short-segment Barrett's esophagus might be milder in nature and more responsive to antisecretory therapy, the researchers said. They noted that severe (grade C/D) esophagitis was strongly linked with both short-segment and long-segment Barrett's esophagus.

The National Institute of Diabetes and Digestive and Kidney Diseases provided funding. The researchers reported having no conflicts of interest.

Key clinical point
GERD without alarm symptoms accounted for 13.5% of all esophagogastroduodenoscopies. Only 5.6% of patients with uncomplicated GERD had suspected Barrett's esophagus of any length, and 1.4% had suspected Barrett's esophagus of 3 cm or longer.

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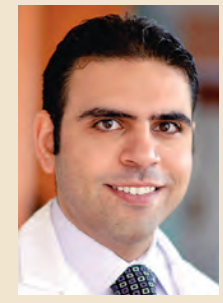
SOURCE: Lin EC et al. Clin Gastroenterol Hepatol. 2019 Apr. doi: 10.1016/j.cgh.2018.08.066.

The utility and cost-effectiveness of screening for Barrett's esophagus with esophagogastroduodenoscopy (EGD) remain contentious issues. National GI societies currently recommend screening in only a limited high-risk population, mainly white men aged 50 or older with chronic GERD and one or more additional risk factors. It is unclear to what degree those guidelines are adhered to in clinical practice. This study by Lin et al. sheds further light on this issue. The investigators showed that a significant proportion (more than 10%) of EGDs were performed for uncomplicated GERD, with less than one-quarter of those patients meeting the minimal criteria for screening for Barrett's esophagus. Among this group, the prevalence of Barrett's esophagus was found to be lower than previously reported. The data offer compelling evidence that screening low-risk patients with uncomplicated GERD by using upper endoscopy is not cost effective, and is at best marginally cost effective if limited to the high-risk group identified by national GI societies. The question arises whether we should abandon screening for Barrett's esophagus altogether.



DR. MANSOUR

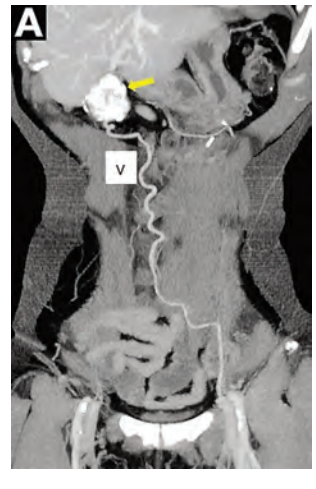
The challenge, however, is that the incidence of esophageal adenocarcinoma continues to rise (albeit at a slower pace in recent years), and 5-year survival of patients diagnosed with esophageal adenocarcinoma remains extremely poor. Therefore, prevention remains the optimal strategy. The solution may lie in adopting a lower-cost screening modality that can replace endoscopy for this purpose, and while many such techniques are under investigation, further studies are required to find a widely applicable alternative to EGD.

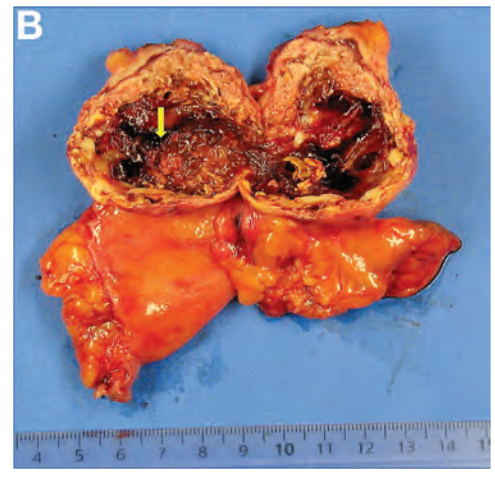
Nabil M. Mansour, MD, is an assistant professor, department of medicine, section of gastroenterology and hepatology, Baylor College of Medicine, Houston. He has no conflicts of interest.

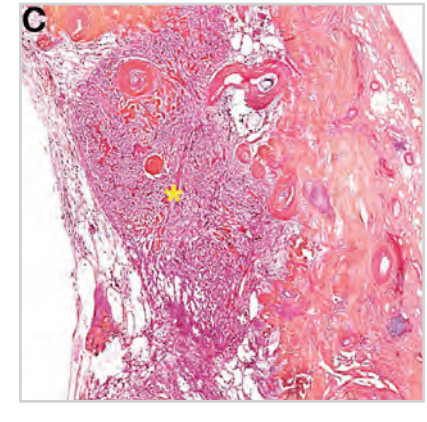
CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

By Sarah Melloul, MD, Mostafa El Hajjam, MD, and Catherine Julié, MD. Published previously in Gastroenterology (2017;152[3]:488-9).







AGA Institute

A 68-year-old woman, asymptomatic, with no medical history, underwent an abdominal computed tomography scan in a traumatic context. An enhanced series (Figure A) revealed a 4-cm cystic mass with tissue and calcified rim components located under the left liver (Figure A, arrow) inside the ligamentum teres. The lesion was supplied by a left hepatic artery branch. The frontal view showed the mass drainage into the left external iliac vein through a long pedicle (the umbilicus vein connected to the left inferior epigastric vein) (v).

A laparoscopic resection of this mass was performed because of the risk of spontaneous hemorrhage linked to the dense tumoral vasculature and the lack of formal histologic diagnosis. During the procedure, the surgeon observed a cystic mass attached to the ligamentum teres between the liver and the umbilicus. At pathologic examination (Figure B), a well-circumscribed largely cystic mass, with a fibrous and calcified shell and hemorrhagic modifications (arrow) was observed. Histologically (Figure C), the fibrous wall contained many large vessels and a small cellular area (star). This area consisted of small nests of moderate-sized monotonous clear cells with normochromatic ovoid nuclei. There was no nuclear atypia and no mitosis. The tumor exhibited an elaborate network of small capillaries. Tumor cells expressed the melanocytic marker HMB45 and smooth muscular actin.

The diagnosis is on page 21.

AGA welcomes new governing board members

Sheila E. Crowe, MD, AGAF, chair of the nominating committee, is pleased to announce that John M. Inadomi, MD, AGAF, joins the presidential lineup for AGA.

John M. Inadomi, MD, AGAF
Dr. Inadomi is a national expert in comparative effectiveness research and colorectal cancer who has lent his expertise to AGA in several capacities over the years, most recently as the clinical research councillor to the board. Dr. Inadomi will serve as vice president, then president elect and will become AGA president after Digestive Disease Week® (DDW) 2021.

The AGA Nominating Committee also appointed the following slate of councillors, which is subject to membership vote.

Maria T. Abreu, MD, AGAF
Councillor-at-Large: Maria T. Abreu, MD, AGAF, is former chair of the AGA Institute Council, which plans AGA's programming for DDW, and a researcher and clinician focusing on inflammatory bowel disease (IBD), microbiome and colorectal cancer.

David A. Katzka, MD
Education and Training Councillor: David A. Katzka, MD, has been very active in AGA's education and practice initiatives, including his recently completed service as the chair of the AGA Institute Clinical Practice Updates Committee. Dr. Katzka received AGA's distinguished clinician award in 2010. His research and clinical work focus on esophageal disorders.

Michael L. Kochman, MD, AGAF
Councillor-at-Large, Growth and Development: Michael L. Kochman, MD, AGAF, takes on this newly created governing board position after successfully leading the AGA Center for GI Innovation and Technology. He is an interventional endoscopist at University of Pennsylvania.

Pending approval by the voting membership, all board members begin their terms after DDW 2019. The voting membership will be sent a ballot to approve the slate of officers on or before March 21, 2019, with a response date of no later than April 20, 2019.

Thank you to our nominating committee members.

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How to get involved in advocacy

Interested in advocacy but not sure how or whether you have time in your busy schedule? AGA has an array of options for how you can be active in advocacy. Some take as little as 5 minutes.

Letter writing. AGA uses GovPredict, an online advocacy platform that allows members to contact their member of Congress with just a few clicks. AGA develops messages on significant pieces of legislation, key efforts in Congress or on issues being advanced by federal agencies that have a great impact on gastroenterology. AGA's ongoing letter writing campaigns can always be found on www.gastro.org/advocacy but be sure to keep an eye out for advocacy emails, AGA eDigest, and social media, so you do not miss your opportunity to take action on timely issues. Share letter writing campaigns with colleagues, as well as posting them on social media.

Meetings with your member of Congress. In-person meetings are an excellent opportunity to share with your member of Congress, or their staff, how the issues that impact gastroenterology affect you, your patients, and your practice. AGA has many resources to help you set up a meeting with your member of Congress, including up-to-date issue briefs, tips and tricks for productive meetings, and webinars on how to host an on-site visit. AGA staff is always more than happy to help you arrange a meeting either in Washington, DC, or your home state. If you are interested in arranging a meeting with your member of Congress, please contact AGA Public Policy Coordinator, Jonathan Sollish, at jsollish@gastro.org or 240-482-3228.

AGA PAC. AGA PAC is a voluntary, nonpartisan political organization affiliated with and supported by AGA. The only political action committee supported by a national gastroenterology society, its mission is to give gastroenterologists a greater presence on Capitol Hill and a more effective voice in policy discussions. AGA PAC supports candidates who support our policy priorities, such as fair reimbursement, cutting regulatory red tape, supporting patient protections, and access to specialty care, and sustained federal funding of digestive disease research. If you are interested in learning more, contact AGA Government and Political Affairs Manager, Navneet Buttar, at nbuttar@gastro.org or 240-482-3221.

Congressional Advocates Program. This grassroots program is aimed at establishing a stronger foundation for our current and future advocacy initiatives by creating state teams to work on advocacy on the local, state, and national levels. Participation can include a wide variety of activities, ranging from creating educational posts on social media to meeting with members of Congress. Members of the Congressional Advocates Program are mentored and receive advocacy training by AGA leadership and staff. Participating members receive an AGA Congressional Advocate Program Certificate, a Digestive Disease Week® (DDW) badge ribbon, policy badge on the AGA Community, and recognition on AGA's website. Applications for the next cycle will be released in 2019.

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Dr. Vaibhav Wadhwa advocates for step therapy reform in Florida

Vaibhav Wadhwa, MD, met with Ms. Laurie Flink, Deputy District Director for Rep. Debbie Wasserman Schultz (FL-23), to discuss AGA's legislative priorities.

Dr. Wadhwa thanked Ms. Flink for Wasserman Schultz's support of the Removing Barriers to Colorectal Screening Act and NIH funding. Dr. Wadhwa also mentioned that Wasserman Schultz is not a cosponsor of the Restoring the Patient's Voice Act and explained in detail about why this is an important resolution that needs to be passed.

Dr. Wadhwa gave examples of patients from his own practice and discussed the challenges they face. Ms. Flink was very interested in hearing about patients with chronic conditions such as inflammatory bowel disease not being able to get the appropriate regimen due to the barriers created by step therapy. Ms. Flink was very appreciative of the visit and stated that these in-person visits along with personal stories about these issues go a long way in helping congressional offices understand the implications that these bills have.

Ms. Flink assured Dr. Wadhwa that she will raise these points with Wasserman Schultz and will discuss cosponsoring the Restoring the Patient's Voice Act once it is reintroduced.

Dr. Wadhwa is a fellow at the Cleveland Clinic Florida in Weston, and is the AGA Congressional Advocates Program state leader for Florida. He is interested in therapeutic endoscopy and advocating for appropriate reimbursement for endoscopic procedures.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

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. Refractory lymphocytic colitis and diarrhea (http://ow.ly/IEn230nXY2Z)

An elderly female with lymphocytic colitis wasn't responding to any treatment provided by her physician, who was trying to avoid a colectomy because of her advanced age. The GI community shared their support with recommendations for therapy options and next steps.

2. Atypical case of enteropathy (http://ow.ly/3Rox30nXY7N)

This physician found mild erosive gastritis, villous blunting and mucosal accumulation of eosinophils up to 55/hpf in an 18-year-old female with a history of nausea, vomiting, nonbloody diarrhea, abdominal pain, and weight loss over the past year. She tested negative for celiac disease and a gluten-free diet provided only partial improvement. The conversation in the Community forum covered potential diagnoses to be considered and recommendations for therapy.

3. Eosinophilic esophagitis with aperistalsis (http://ow.ly/8Uir30nXYbW)

A 21-year-old male presented progressive dysphagia due to eosinophilic esophagitis with a weight loss of 17 pounds in 2 months. A panendoscopy revealed a hiatal hernia and aperistalsis of the esophagus, with normal inferior and superior sphincter pressures. No changes were observed recently; he is being managed with prokinetics and remains asymptomatic.

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

Continuing board certification vision report includes many sound recommendations on MOC

The Continuing Board Certification: Vision for the Future Commission submitted its final report to the American Board of Medical Specialties (ABMS) Board of Directors. The draft reflected many of the issues AGA has raised with ABIM over the years and our comments on the draft report.

Here's a link to the full report: https://visioninitiative.org/commission/final-report/

Key wins:

- Commission recommended the term "Maintenance of Certification" be abandoned.
- "Emphasis on continuing certification must be focused on the availability of curated information that helps diplomates deliver improved clinical care ... traditional infrequent high-stakes assessments no matter how psychometrically valid, is viewed as inappropriate as the future direction for continuing certification."
- The Commission believes ABMS Boards need to engage with diplomates on an ongoing basis instead of every 2, 5, or 10 years.
- The ABMS Board must offer an alternative to burdensome highly secure, point-in-time examinations of knowledge.
- ABMS and ABMS Boards must facilitate and encourage independent research to build on the existing evidence base about the value of continuing certification.

MOC and AGA's approach to reform are topics of much discussion on the AGA Community.

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Include the AGA Research Foundation in your future plans

You can continue helping young investigators after your lifetime. Gifts to charitable organizations, such as the AGA Research Foundation, in your future plans ensure your support for our mission continues even after your lifetime. Here are fast facts about planned giving:

1. Planned gifts are complicated and confusing.
They don't have to be. There are many types of planned gifts: Most are simple and affordable, like a gift in your will or living trust. You just need to find the one that best meets your needs.

2. Planned gifts are only for the wealthy.
Anyone can make a planned gift. Gifts of all sizes make a difference at the AGA Research Foundation. In fact, you may even be able to make a bigger impact than you thought possible when you make a planned gift.

3. Wills are only for older adults.
Having a plan for the future is important—no matter your age. An estate plan makes your wishes known and provides your loved ones with peace of mind.

By including a gift to the AGA Research Foundation in your will, you create a legacy of support at the AGA Research Foundation.

Want to learn more about including a gift to the AGA Research Foundation in your future plans? Visit our website at https://gastro.planmylegacy.org or contact Harmony Excellent at 301-272-1602 or hexcellent@gastro.org.

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The New Gastroenterologist seeks its next editor in chief

AGA's cutting-edge, trainee and early-career focused e-newsletter *The New Gastroenterologist* (TNG) is seeking applications for the position of editor-in-chief (EIC). The role will facilitate the communication of the latest clinical advances among peers and build strong leadership skills, managing editorial responsibilities, as well as working with reviewers and fellow editors at AGA's journals.

The term is from Oct. 1, 2019 to Sept. 30, 2022, with a transition period starting July 2019.

About TNG

TNG content covers highly relevant clinical topics, such as endoscopic management of obesity and quality metrics on colonoscopy. Also included in each issue are articles that focus on career pathways, financial and legal matters, perspectives from private practice, and other topics that are relevant to early-career gastroenterologists.

Honorarium

The EIC will receive an annual honorarium of $5,000.

Qualifications

- AGA member, between second year of fellowship and 5 years postfellowship.
- Experience identifying and promoting newsworthy content that is relevant to the trainee and early-career GI community, as well as excellent judgment that expands the outstanding reputation of TNG and AGA.
- Experience in medical, scientific or news-related publishing is preferred, but not required.
- Familiarity with AGA and its priorities, activities and stances on important issues is ideal, preferably via past volunteer member experience with the association.
- The EIC must be able to devote sufficient time to TNG matters and may not accept editorial appointments to competing publications during their tenure as EIC.

To view the full request for applications, please visit https://www.gastro.org/news/the-new-gastroenterologist-seeks-its-next-editor-in-chief.

If you have questions, please contact Ryan Farrell, managing editor, *The New Gastroenterologist*, at rfarrell@gastro.org.

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DDSEP eight
Digestive Diseases Self-Education Program

Answers

Q1. Correct Answer: C

Rationale: ICP has a 60%-70% recurrence rate, and therefore, this patient is at high risk of recurrence. Ursodeoxycholic acid (UDCA) has been shown to reduce pruritus and improve bile acid levels and liver-associated enzymes. There is also evidence that UDCA is safe late in pregnancy and likely improves fetal outcomes. Cholestyramine is not as effective as UCDA at reducing pruritus, reducing bile acid levels, or normalizing aminotransferase. In addition, babies are delivered closer to term with UDCA as opposed to cholestyramine. Hydroxyzine improves pruritus but can aggravate respiratory issues in preterm babies and is not recommended in ICP. Given these findings, UDCA is considered first-line therapy in treatment of ICP. A recent study showed that the perinatal mortality is decreased with delivery of the baby at 36 weeks' gestation, or if ICP develops past 36 weeks, delivery with onset of symptoms. Thus, optimal management if her current pregnancy mimics the previous pregnancy is for UDCA to be given with development of symptoms with planned delivery at approximately 36-37 weeks gestation.

References

1. Bacq Y, Sentilhes L, Reyes HB, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology. 2012;143(6):1492-501.
2. Kondrackiene J, Beurers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology. 2005;129(3):894-901.
3. Puljic A, Kim E, Page J, et al. The risk of fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Am J Obstet Gynecol. 2015;212(5):667e1-5.

Q2. Correct Answer: C

Critique: Factors raising suspicion for Zollinger-Ellison syndrome include recurrent peptic ulcer disease, multiple ulcers, post-bulbar ulcer, non-*H. pylori*/non-NSAID-related duodenal ulcer, diarrhea, erosive esophagitis, and family or personal history of multiple endocrine neoplasia type 1. The patient in this question presents with duodenal ulcer without *H. pylori* or NSAID use, erosive esophagitis, and diarrhea, which raises suspicion for hypergastrinemia.

His laboratory evaluation also showed hypercalcemia, which may be due to hyperparathyroidism, a condition related to MEN I. The initial test to obtain when gastrinoma is suspected includes a fasting serum gastrin level. In follow-up of gastrin elevations, a gastric pH assessment should be performed and, depending on these results, a secretin stimulation test may be useful. Routine repeat upper endoscopy is not indicated after hemostasis of duodenal ulcer bleeding.

A restrictive transfusion strategy with a hemoglobin threshold of 7 g/dL has been shown to result in improved clinical outcome compared to a liberal transfusion strategy. While sucralfate may help the healing of duodenal ulcers, it is not the first-line therapy for long-term secondary prevention.

References

1. Roy PK, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. Medicine (Baltimore) 2000;79:379.
2. Murugesan SV, Varro A, Pritchard DM. Review article: Strategies to determine whether hypergastrinaemia is due to Zollinger-Ellison syndrome rather than a more common benign cause. Aliment Pharmacol Ther 2009;29:1055-68.
3. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013 Jan 3;368(1):11-21.

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Most treatments can be continued

IBD care *from page 1*

medications during pregnancy because they feared harm to the fetus. In doing so, these patients actually risked greater disease activity, perinatal flares, and adverse pregnancy outcomes.

Therefore, the AGA in partnership with the Crohn's & Colitis Foundation, the Society for Maternal-Fetal Medicine, and Girls With Guts crafted a standardized, evidence-based care pathway for health care providers from diverse disciplines who treat women with IBD in all stages of family planning. Its authors recommended that a maternal-fetal medicine specialist oversee obstetric care whenever possible. A gastroenterologist should continue IBD care by seeing the patient once during the first or second trimester and thereafter depending on IBD severity. The patient should receive a "clear and easily understandable consensus plan" for managing complex care during and after pregnancy, according to the pathway.

Aminosalicylates, biologics, and immunomodulators can be continued during pregnancy and delivery. Biologics have not shown teratogenicity in large studies, but monotherapy is preferred to reduce infection risk in infants. Clinicians should calculate weight-based doses according to prepregnancy weight. Doses can be tweaked to achieve minimal trough levels near delivery.

During pregnancy, patients should stop antidiarrheal therapy with loperamide and diphenoxylate when possible. Proinflammatory mediators are known to damage hippocampal neurogenesis and neuronal cytoarchitecture during brain development, so patients should understand the need for good inflammatory control during pregnancy. However, biologic therapy is preferred, and patients should use corticosteroids adjunctively only if needed for flares.

The usual indications guide the choice between a vaginal or cesarean delivery, the pathway states. Vaginal delivery often is possible for patients without active perineal disease, while cesarean is recommended for women with prior perineal surgery or active perineal disease or rectovaginal fistulas. The perineal area can be examined for active disease during the routine visit for group B streptococcus screening culture at 35-37 weeks' gestation. For women who have had ileal-pouch anal anastomosis surgery, mode of delivery does not seem to affect pouch function, but cesarean delivery is thought to prevent anal sphincter injury and the accompanying risk of incontinence.

For ostomy patients, stretching of the abdominal wall during pregnancy can lead to stomal problems, such as displacement, enlargement, retraction, stenosis, and prolapse. A nutritionist can help ostomy patients avoid excess weight gain, and a colorectal surgeon and ostomy/wound nurse can help coordinate postpartum care. If cesarean delivery is needed, simply covering the ostomy with gauze sufficiently protects the operative field.

Since IBD increases the risk of venous thromboembolism, clinicians should consider prophylactic anticoagulation after cesarean delivery and during a hospitalization for IBD flares, according to the care pathway. Breastfeeding women can receive unfractionated heparin, low-molecular-weight heparin, or warfarin up to 3-6 weeks post partum, but they should not receive oral direct thrombin or factor Xa inhibitors.

In addition, most IBD medications are either undetectable in breast milk or are secreted at such low concentrations that they pose no known risk to infants. Therefore, patients can continue IBD medications after delivery – except methotrexate, which has not been sufficiently studied to assess its safety. Breastfeeding women with IBD should avoid using fenugreek to increase milk production, since it can cause diarrhea and bleeding.

Finally, infants should not receive live vaccines during the first 6 months after birth if their mothers received biologics besides certolizumab during the third trimester, the pathway notes. In the United States, this applies only to the oral rotavirus vaccine.

For more information about the care pathway and resources for your patients, visit IBDParenthoodProject.org.

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SOURCE: Mahadevan U et al. Gastroenterology. 2019 Jan 15. doi: 10.1053/j.gastro.2018.12.022.

AGA CLINICAL PRACTICE UPDATE

Switching between biologics and biosimilars in inflammatory bowel disease

BY AMY KARON
MDedge News

Patients with inflammatory bowel disease (IBD) will soon have access to new biosimilars to infliximab, adalimumab, and other monoclonal antibodies, experts wrote in an American Gastroenterological Association clinical practice update.

"It is anticipated that biosimilars for IBD are here to stay," wrote Laura E. Raffals, MD, of the Mayo Clinic in Rochester, Minn., and her associates in Clinical Gastroenterology and Hepatology. "Provided that the regulatory pathway remains rigorous and postmarketing surveillance is performed adequately, clinicians and patients can be reassured that these agents will provide the same well-described effectiveness for moderate to severe Crohn's disease and ulcerative colitis, without new safety concerns."

Evidence supports the use of biosimilars in IBD, but switching patients in stable remission on infliximab (Remicade) to a biosimilar, namely infliximab-dyyb (Inflectra), should remain a case-by-case choice, according to the clinical practice update. Pending more safety data, the update's authors recommended against nonmedical switches during pregnancy and urge special attention when considering whether to switch children.

Biologics have revolutionized IBD treatment, but at a steep price. As patents expire, companies have developed biosimilar agents that aim to conserve safety and efficacy at lower cost. Studies support this idea, although whether initiating or switching to biosimilars will save patients (versus hospitals or payers) money "remains to be seen," the practice update states.

Pending more safety data, the update's authors recommended against nonmedical switches during pregnancy and urge special attention when considering whether to switch children.

The FDA approval process for biosimilars is more rigorous than that for generics, but it skips the multiple phases of clinical trials required to approve reference biologics. Instead, the FDA requires robust evidence that the biosimilar has comparable structure, function, immunogenicity, animal toxicity, pharmacokinetics and pharmacodynamics, and clinical safety and efficacy in humans. Under U.S. law, a biosimilar cannot be FDA approved if its clinically active components differ from the reference product or it shows clinically meaningful differences in safety, potency, or purity.

So far, five biosimilars have been approved by the FDA for use in IBD, although not all are on the market yet: infliximab-dyyb (Inflectra), adalimumab-atta (Amjevita), infliximab-abda (Renflexis), adalimumab-adbm (Cyltezo), and infliximab-qbtx (Ixifi). Most postmarketing studies of biosimilar use involved patients on stable doses of Remicade who switched to biosimilar infliximab-dyyb (Inflectra).

The best known of these studies is the double-blind, randomized NOR-SWITCH trial, in which patients with Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, or chronic plaque psoriasis on Remicade either continued it or switched to biosimilar infliximab-dyyb (Inflectra). At week 52, both safety and the likelihood of worsening disease activity were similar regardless of treatment. The study was not powered to assess subgroup outcomes in Crohn's disease or ulcerative colitis, the practice update notes.

More recently, the results of the 16-week SECURE trial also indicated that switching to infliximab-dyyb (Inflectra) was safe and well tolerated by patients with remitted IBD. However, the FDA has not yet designated any biosimilar as "interchangeable" with an approved biologic confirmed safe in multiple switches. As a result, state laws prohibit patients from being switched to a biosimilar without notification. Both the NOR-SWITCH and SECURE trials were done in Europe.

Clinicians also must understand that antidrug antibodies to originator and biosimilar infliximab cross-react with each other, the experts emphasized. Switching patients with antibodies to Remicade or a biosimilar to the other product therefore risks an immediate hypersensitivity reaction, including life-threatening anaphylaxis.

The authors disclosed no external funding sources. One author disclosed ties to AbbVie, Janssen, Pfizer, Merck, Samsung Bioepis, and Amgen. The rest reported no conflicts of interest.

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SOURCE: Raffals LA et al. Clin Gastroenterol Hepatol. 2018 Sep 6. doi: 10.1016/j.cgh.2018.08.064.

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 14: Cystic and calcified PEComa of the ligamentum teres

PEComas are tumors derived from epithelioid perivascular cells that typically coexpress smooth muscle and melanocytic markers. The family of PEComas includes angiomyolipoma, clear cell "sugar" tumor, and lymphangioleiomyomatosis. Some of these tumors may be associated with tuberous sclerosis complex. PEComas of the ligamentum teres (also called in this location "clear cell myomelanocytic tumors") are rare, but the ligamentum teres location is the most classic in children. Thirteen cases have been reported in the literature, within or in the immediate vicinity of falciform ligament/ligamentum teres.[1-3] There was a marked female predominance with a mean age of 20 years (range, 3-54 years), a mean size of 8 cm (range, 5-20 cm), and a significant risk of metastasis (3 of 13 cases). Many of the lesions were calcified and had hemorrhagic and cystic alterations.

In the absence of established malignancy criteria, PEComas must be considered to have an uncertain malignant potential, requiring surgical resection and long-term monitoring. A mass of the ligamentum teres should always lead to consideration of the diagnosis of PEComa, even in adults, and even with cystic presentation. Moreover, most frequently, other tumors of the ligamentum teres are malignant (local extension of hepatocellular carcinoma, metastatic adenocarcinoma of gastrointestinal or gynecological origin). The patient was free of disease at 6 months' follow-up.

References

1. Folpe AL, Goodman ZD, Ishak KG, et al. Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. Am J Surg Pathol. 2000;24:1239-46.
2. Folpe AL, Mentzel T, Lehr HA, et al. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin. Am J Surg Pathol. 2005;29:1558-75.
3. Alaggio R, Cecchetto G, Martignoni G, et al. Malignant perivascular epithelioid cell tumor in children: description of a case and review of literature. J Pediatr Surg. 2012;47:31-40.

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Survey: CRC diagnosis often delayed or initially missed in patients under age 50

BY SHARON WORCESTER
MDedge News

The incidence of colorectal cancer in patients aged 20-49 years is increasing, but the diagnosis is often delayed in this age group because of a failure by both patients and physicians to recognize the symptoms as related to CRC, a survey suggests.

Of 1,195 colorectal cancer (CRC) patients or survivors aged under 50 years who responded to the web-based survey, 63% waited between 3 and 12 months before visiting their doctor after experiencing symptoms, including bloating, constipation, rectal bleeding, blood in stool, abdominal pain, flatulence, fatigue, or nausea and vomiting, Ronit I. Yarden, PhD, reported during a press conference highlighting data to be presented at the upcoming American Association for Cancer Research (AACR) annual meeting in Atlanta.

More than half of the respondents (56%) had at least three symptoms and still waited at least 3 months before visiting a doctor.

"And almost one in four waited at least a year to visit their doctor or other provider," said Dr. Yarden, director of medical affairs for the Colorectal Cancer Alliance in Washington, which conducted the survey.

When patients did seek medical care, they often were initially misdiagnosed. In fact, 67% of the respondents reported having seen at least two physicians, with some seeing more than four physicians, before being diagnosed correctly with CRC, she said, noting that among the most common misdiagnoses were hemorrhoids and inflammatory bowel disease.

Some patients reported seeing more than four physicians, before being diagnosed correctly with CRC.

DR. YARDEN

The delays in treatment and correct diagnoses have life-threatening implications; data show that, while the overall incidence of CRC is declining, the incidence in younger adults has increased. According to the American Cancer Society, most CRC patients over the age of 50 years are diagnosed in the early stages of disease, whereas 71% of the young-onset survey respondents were diagnosed at stage III or IV, Dr. Yarden said.

This is important, because 5-year survival is only 70% for stage III disease, and is less than 50% for stage IV disease. One in four survey respondents was diagnosed at stage IV, she said.

The survey included young-onset patients and survivors and was administered over social media to track the self-reported clinical, psychosocial, financial, and quality of life experiences of "this often-overlooked group," she said.

The majority of participants (57%) were diagnosed between the ages of 40 and 49 years, a third were diagnosed between the ages of 30 and 39, and about 10% were diagnosed before the age of 30.

The findings underscore the need for greater awareness that "colorectal cancer, which is one of the most preventable diseases, can happen in younger adults," Dr. Yarden said, also noting that extended screening is needed "if we want to beat this disease."

John D. Carpten, PhD, the AACR meeting program chair and press conference comoderator, agreed that the findings could have significant policy implications, as many screening recommendations for CRC call for screening beginning at age 50 years.

"So for those individuals who are diagnosed with colon cancer in their 30s or 40s, this raises a potentially significant problem," he said. "Additional studies need to be done to actually identify the factors influencing these early-onset cancers. ... Hopefully that will improve our ability to detect these cancers earlier and to identify the most appropriate and effective ways to treat these cancers – particularly given that they tend to be diagnosed at more advanced stages."

Work is also needed to help ensure access to the most appropriate care for younger patients – a concern related to disparities in health care access, he said, noting that the AACR meeting with "have a strong emphasis on disparities."

Disparities can be related to race/ethnicity, rural versus urban setting, and socioeconomic factors, but they can also be related to age – which might be a particular problem in the case of early-onset CRC, he said.

Adolescent and young-adult patients, in particular, represent "sort of a new disparity group," and "can sometimes get lost in the system," said Dr. Carpten, professor and chair of translational genomics and director of the Institute of Translational Genomics at the University of Southern California, Los Angeles.

This study was funded by the Colorectal Cancer Alliance. Dr. Yarden reported having no conflicts of interest.

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SOURCE: Yarden RI et al. AACR 2019, Abstract preview.

Personalized approach needed

Distinct *from page 1*

ring histology and less likely to have adenomatous polyposis coli (APC) mutations, according to senior study author Jonathan M. Loree, MD, and his coinvestigators at The University of Texas MD Anderson Cancer Center, Houston.

"We need to appreciate that there are unique biologic subtypes within young patients that may affect how their cancers behave and may require a personalized approach to treatment," Dr. Loree said in a press statement. "Going forward, special clinical consideration should be given to, and further scientific investigations should be performed for, both very young patients with colorectal cancer and those with predisposing medical conditions."

The incidence of young-onset CRC has increased 1%-3% annually in recent years, Dr. Loree and colleagues wrote in their report.

Although smaller studies have characterized molecular features of CRC in younger patients, there has so far been no comprehensive molecular characterization of these patients, they added. Accordingly, the investigators conducted a retrospective analysis that included more than 36,000 patients in four different patient cohorts.

Patients under 50 years more likely had synchronous metastases ($P = .009$), more likely had primary tumors in the distal colon and rectum (P less than .0001), and were more likely to be MSI-high ($P = .038$), compared with their older counterparts, Dr. Loree and coauthors reported.

BRAF V600 mutations were infrequent in patients under 30 years of age, at a prevalence of 4% or less, increasing to a high of 13% in patients aged 70 years or older (P less than 0.001), investigators also reported.

Very young patients, or those aged 18-29 years, had a higher prevalence of signet-ring histology, compared with the other age groups ($P = .0003$), and they had a nearly fivefold increased odds of signet-ring histology compared with patients in the 30-49-year age range, investigators wrote.

There were also considerably fewer APC mutations in the patients younger than 30 years, compared with older patients in the young-onset CRC group, with an odds ratio of 0.56 (95% confidence interval, 0.35-0.90; $P = .015$).

Hispanic patients were significantly overrepresented in the under-30-years age group ($P = .0015$), according to the report.

For patients under 50 years who also had inflammatory bowel disease, odds of mucinous or signet-ring histology were higher (OR, 5.54; 95% CI, 2.24-13.74; $P = .0004$), and odds of APC mutations were lower (OR, 0.24; 95% CI, 0.07-0.75; $P = .019$), compared with younger patients with no such predisposing conditions.

"These notable differences in very young patients with CRC and those with predisposing conditions highlight that early-onset CRC has unique subsets within the population of patients younger than 50 years," Dr. Loree and coauthors concluded.

Support to investigators in the study came from the National Cancer Institute, National Institutes of Health, and the MD Anderson Colorectal Cancer Moon Shot Program. One coinvestigator reported disclosures related to Roche, Genentech, EMD Serono, and several othr pharmceutical companies

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SOURCE: Willauer AN et al. Cancer. 2019 Mar 11. doi: 10.1002/cncr.31994.

Reduced all-cause mortality

DAAs *from page 1*

DAA treatment and 2,551 who remained untreated at a median follow-up of more than 31 months. The median patient age was 56 years, and 53% were men.

Treatment with DAAs reduced risk of hepatocellular carcinoma when compared with no DAA treatment, with a hazard ratio of 0.66 (95% confidence interval, 0.46-0.93), and reduced risk of all-cause mortality, with an HR of 0.48 (95% CI, 0.33-0.70), investigators reported in a multivariable analysis that adjusted for variables including age, sex, fibrosis score, HCV genotype, alcohol use, and more.

'Our results support urgent treatment of patients with advanced liver disease and extension of the follow-up of treated patients with less severe disease to assess the long-term clinical effect of direct-acting antiviral treatment.'

"These inverse associations persisted in the subgroup of patients who achieved a sustained virological response, whereas those who did not achieve a sustained virological response were a higher risk for hepatocellular carcinoma," said the investigators, led by Fabrice Carrat, PhD, of Sorbonne Université, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris.

Sustained virologic response was observed in 94% of patients who had known response status and sufficient follow-up, investigators said.

In patients with cirrhosis at baseline, DAA treatment had a similarly strong association with reduced hepatocellular carcinoma and mortality, with a sustained virologic response rate of 92% in those for whom sufficient data were available, they said.

There was no evidence for an increased risk of hepatocellular carcinoma on treatment, with an adjusted HR of 0.74 (95% CI, 0.49-1.13; $P = 0.17$), they added.

"Our results support urgent treatment of patients with advanced liver disease and extension of the follow-up of treated patients with less severe disease to assess the long-term clinical effect of direct-acting antiviral treatment," Dr. Carrat and colleagues said in a commentary on their results.

However, the long-term effect of DAAs on liver decompensation has yet to be clarified, they added, noting that their study excluded patients with decompensated cirrhosis or a history of hepatocellular carcinoma.

Funding for the study came from INSERM, Agence Nationale de la Recherche, DGS (Direction Générale de la Santé), MSD, Janssen, Gilead, AbbVie, Bristol-Myers Squibb, and Roche. Dr. Carrat reported personal fees from Imaxio not related to the present study. Coauthors provided additional disclosures related to Gilead, AbbVie, Bristol-Myers Squibb, MSD, and Janssen, among others.

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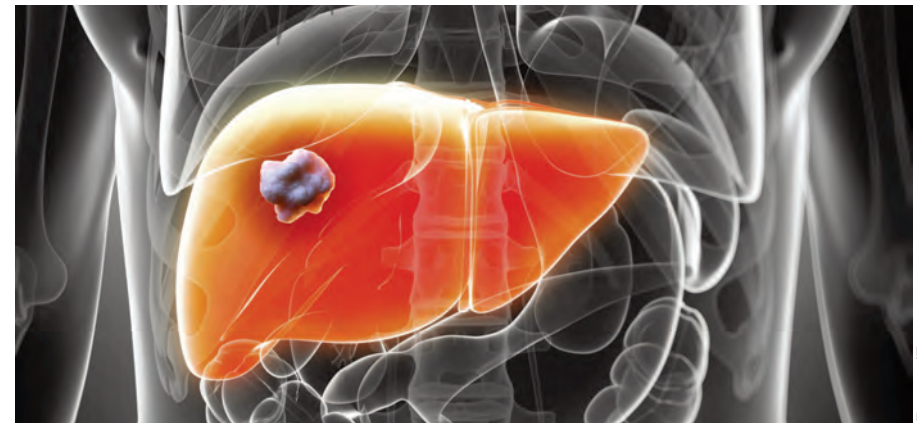
SOURCE: Carrat F et al. Lancet. 2019 Feb 11. doi: 10.1016/S0140-6736(18)32111-1.



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PERSPECTIVE

Best evidence to date of reduced complications

This study provides "substantive evidence" that curing hepatitis C virus with all-oral direct-acting antiviral regimens provides clinical benefits, according to Raymond T. Chung, MD, and his coauthors of a related editorial.

Investigators in this study provide the best evidence so far in support of guidelines that advise direct-acting antiviral (DAA) treatment for all patients with chronic hepatitis C virus (HCV) infection, the editorial's authors stated.

Results of the French study provide a strong counterpoint to the findings of a recent Cochrane review of DAA trials that could not confirm or reject whether DAAs had effects on long-term morbidity and mortality related to HCV, added Dr. Chung and his coauthors. "Finally, they provide credence to the achievability of the goals set out by the World Health Organization (WHO), not only to eliminate HCV but also to substantially reduce its complications."

The WHO targets were established in light of earlier evidence that sustained virologic responses are linked to reductions in hepatocellular carcinoma, liver transplantation, and mortality, they said.

"In view of the high sustained virological response and excellent tolerability achieved with DAAs, it seemed highly plausible to envision reductions in chronic HCV infection–related complications with these drugs," they said in reference to the study by Carrat and colleagues.

This editorial appearing in the Lancet was authored by Raymond T. Chung and his colleagues at the Liver Center, Gastrointestinal Division, Massachusetts General Hospital, Boston. Dr. Chung provided disclosures related to AbbVie, Gilead, Merck, Bristol-Myers Squibb, Roche, Janssen, and Boehringer Ingelheim.

Cirrhosis: Women survive hospitalization more often than men

BY WILL PASS
MDedge News

Women hospitalized with cirrhosis are less likely to die in the hospital than are men, according to a retrospective analysis of more than half a million patients.

Although women more often had infections and comorbidities, men more often had liver decompensation, which contributed most significantly to their higher mortality rate, reported lead author Jessica Rubin, MD, of the University of California, San Francisco, and her colleagues.

Their findings add to an existing body of knowledge about sex-related differences in chronic liver disease. Women are less likely to develop chronic liver disease; however, when women do develop disease, it often follows a unique clinical course, with milder early disease followed by more severe end-stage disease, meaning many women are too sick for a transplant, or die on the waiting list.

"The reasons behind this 'reversal' in [sex] disparities is unknown," the investigators wrote in Journal of Clinical Gastroenterology.

Considering recent findings that showed a correlation between hospitalization and mortality rates in chronic liver disease, the investigators believed that a comparison of hospital-related outcomes in men and women could explain why women apparently fare worse when dealing with end-stage disease.

The retrospective, cross-sectional study involved 553,017 patients (median age, 57 years) who were hospitalized for cirrhosis between 2009 and 2013. Data were drawn from the National Inpatient Sample (NIS). Inpatient mortality was the primary outcome.

In agreement with previous findings, the minority of patients were women (39%). Against expectations, however, women had a significantly lower mortality rate than that of men (5.7% vs. 6.4%; multivariable analysis odds ratio, 0.86). Better survival was associated with lower rates of decompensation (Baveno IV criteria; 34% vs. 38.8%) and other cirrhosis complications, such as hepatorenal syndrome, variceal bleeding, ascites, and spontaneous bacterial peritonitis. The only cirrhosis complica-

Continued on next page

Ultrasound method may predict liver complications in pediatric transplant

BY ANDREW D. BOWSER
MDedge News

HOUSTON – An ultrasound method for assessing liver stiffness might be useful for predicting which pediatric patients will develop a life-threatening complication of hematopoietic stem cell transplantation.

Shear wave elastography values predicted severe hepatic sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) at least 4 days before standard diagnostic criteria in most patients treated in a small, prospective, two-center study, Sherwin S. Chan, MD, PhD, said at the Transplantation & Cellular Therapy Meetings.

Early identification of SOS/VOD using elastography could be beneficial in light of data showing that timing is critical in the administration of defibrotide, a treatment recommended for severe and very severe patients, according to Dr. Chan, vice chair of radiology for the University of Missouri at Kansas City.

Key clinical point
Increased shear wave elastography velocity predicted severe SOS/VOD, with a cutoff value of 1.65 m/s being 92% sensitive and 67% specific for the complication.

"If you're able to initiate it early, you can really increase day 100 survival," Dr. Chan said in an oral presentation.

The data presented included 54 pediatric patients undergoing transplantation at one of two institutions.

At one site, the patients underwent shear wave elastography evaluation 10 days before the conditioning regimen began, and again at 5 and 14 days after the transplant. At the other site, patients with suspected SOS/VOD were enrolled and underwent elastography every other day for up to 10 exams.

Those are very different imaging protocols, Dr. Chan acknowledged in his presentation, noting that the studies started independently and data were pooled as investigators at the two institutions became aware of one another's work.

A total of 16 patients, or 30%, developed SOS/VOD, Dr. Chan reported. Of those 16 cases, 12 (75%) were severe or very severe by the recent European Society for Blood and Marrow Transplantation (EBMT) criteria.

Increased shear wave elastography velocity was the best predictor of severe SOS/VOD, according to Dr. Chan, with a cutoff value of 1.65 m/s being 92% sensitive and 67% specific for severe SOS/VOD.

That threshold was passed at least 4 days before severe grading or death in 9 out of the 12 severe cases, he added.

Andrew D. Bowser/MDedge News

Dr. Sherwin S. Chan of the University of Missouri, Kansas City, presented his findings at the Transplantation & Cellular Therapy Meetings.

Accordingly, a prospective, multicenter trial has been initiated at a number of U.S. centers to investigate whether the findings of this study are generalizable to other patient populations, Dr. Chan said at the meeting held by the American Society of Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research. At this meeting, the American Society for Blood and Marrow Transplantation announced a new name for the society: American Society for Transplantation and Cellular Therapy.

That prospective, multicenter trial is supported by Jazz Pharmaceuticals, according to Dr. Chan, who reported consulting with Jazz Pharmaceuticals in his disclosure statement.

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SOURCE: Chan SS et al. TCT 2019, Abstract 55.

Continued from previous page

tion more common in women than men was hepatic encephalopathy (17.8% vs. 16.8%). Because of fewer complications, fewer women required liver-re Raymond T. Chung lated interventions, including transjugular intrahepatic portosystemic shunt (0.8% vs. 1.0%), upper endoscopy (12.8% vs. 13.0%), or paracentesis (17.6% vs. 20.6%).

While less frequent complications and a lower mortality rate might suggest that women were admitted with better overall clinical pictures, not all data supported this conclusion. For instance, women were more likely to have noncirrhosis comorbidities, including diabetes, hypertension, heart failure, stroke, and cancer. Furthermore, women had a higher rate of acute bacterial infection than that of men (34.9% vs. 28.2%), although this disparity should be considered in light of urinary tract infections (UTIs), which were significantly more common among women (18.8% vs. 8.0%).

"Interestingly, infections were a stronger predictor of inpatient mortality in women than men," the investigators wrote. "Despite this, women in our cohort were less likely to die in the hospital than men."

Additional analysis revealed etiological differences that may have contributed to differences in mortality rates. For instance, women less often had liver disease due to viral hepatitis (27.6% vs. 35.2%) or alcohol (24.1% vs. 38.7%). In contrast, women more often had autoimmune hepatitis (2.5% vs. 0.4%) or cirrhosis due to unspecified or miscellaneous reasons (45.7% vs. 25.7%).

"Our data suggest that differential rates of ongoing liver injury – including by cofactors such as active alcohol use – explain some but not all of the [sex] difference we observed in hepatic decompensation," the investigators wrote, before redirecting focus to a clearer clinical finding. "The poor prognosis of decompensated cirrhosis ... provides a reasonable explanation for the higher rates of in-hospital mortality seen among men versus women," they concluded.

Considering the surprising findings and previously known sex disparities, Dr. Rubin and her colleagues suggested that more research in this area is needed, along with efforts to deliver sex-appropriate care.

"The development of [sex]-specific cirrhosis management programs – focused on interventions to manage the interaction between cirrhosis and other common comorbidities, improving physical function both before and during hospitalization, and postacute discharge programs to facilitate resumption of independent living – would target differential needs of women and men living with cirrhosis, with the ultimate goal of improving long-term outcomes in these patients," the investigators wrote.

The study was funded by a National Institute on Aging Paul B. Beeson Career Development Award in Aging and a National Institute of Diabetes and Digestive and Kidney Diseases National Research Service Award hepatology training grant. The investigators declared no conflicts of interest.

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SOURCE: Rubin J et al. J Clin Gastroenterol. 2019 Feb 22. doi: 10.1097/MCG.0000000000001192.

Big pharma says it can't drop drug list prices alone

BY GREGORY TWACHTMAN
MDedge News

Top pharmaceutical executives expressed willingness to lower the list prices of their drugs, but only if there were cooperation among all sectors to reform how drugs get from manufacturer to patient.

That theme was common in the testimony of seven pharmaceutical executives before the Senate Finance Committee during a Feb. 26 hearing.

"We are in a system that used to be fit for purpose and really drove enormous savings over the last few years but it is no longer fit for purpose," Pascal Soriot, executive director and CEO of AstraZeneca, testified before the committee. "It's one of those situations where nobody in the system can do anything, can fix it by themselves."

'Due to the structure of the Part D benefit design, patients are charged out-of-pocket costs on a medicine's list price, which does not reflect the market-based rebates that Medicare receives,' AbbVie Chairman and CEO Richard Gonzalez testified.

The problem, the executives agreed, is the financial structure of drug delivery that ties list prices and their associated rebates to formulary placement.

"If you went back a few years ago, when we negotiated to get our drugs on formulary, our goal was to have the lowest copay by patients," Kenneth Frazier, chairman and CEO of Merck, testified before the committee. "Today, the goal is to pay into the supply chain the biggest rebate. That actually puts the patient at a disadvantage since they are the only ones that are paying a portion of the list price. The list price is actually working against the patient."

When asked why the list prices of prescription drugs are so high, Olivier Brandicourt, MD, CEO of Sanofi, said, "We are trying to get formulary position with those high list price-high rebate. It's a preferred position. Unfortunately that preferred position doesn't automatically ensure affordability."

Mr. Frazier added that, if a manufacturer brings a product "with a low list price in this system, you get punished financially and you get no uptake because everyone in the supply chain makes money as a result of a higher list price."

Executives noted that, when accounting for financial incentives such as rebates, discounts, and coupons, net prices for pharmaceuticals have actually come down even as list prices are on the rise to accommodate competition on formulary placement.

But that is obscured at the pharmacy counter, where patients are paying higher and higher out-of-pocket costs because more often than not, payment is tied to the list price of the drug, not the net price after all rebates and other discounts have been taken into consideration.

This is a particular problem in Medicare Part D, said AbbVie Chairman and CEO Richard Gonzalez.

"Due to the structure of the Part D benefit design, patients are charged out-of-pocket costs on a medicine's list price which does not reflect the market-based rebates that Medicare receives," he testified.

Despite acknowledging that this is a problem, the executives gathered were hesitant to commit to simply lowering the list prices, or anything for that matter.

The closest the panel came to a commitment to lowering the list prices of their drugs was to do so if all rebates went away in both the public and private sector.

But beyond that, the pharma executives continued to assign responsibility for high out-of-pocket drug costs to other players in the health care system, adding that the only way to change the situation would be to have everyone come to the table simultaneously.

"I understand the dissatisfaction with our industry," Mr. Frazier said. "I understand why patients are frustrated because they need these medicines and they can't afford them. I would pledge to do everything that we could, but I would urge you to recognize that the system itself is complex and it is interdependent and no one company can unilaterally lower list prices without running into financial and operating disadvantages that make it impossible to do that. But if we all bring the parties together around the table with the goal of doing what's best for the patient, I think we can some up with a system that works for all Americans."

Ultimately, the panel suggested, legislation is going to be required to change the system.

Courtesy Senate Finance Committee

Opening remarks were by Senator Chuck Grassley of Iowa Chairman, Senate Finance Committee Hearing on Drug Pricing in America: A Prescription for Change, Part II.

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PRACTICE MANAGEMENT TOOLBOX: Implementation of a population-based cirrhosis identification and management system

BY FASIHA KANWAL, MD, MSHS, AGAF, SRIKAR MAPASKHI, MD, DONNA SMITH, MED, TAMAR TADDEI, MD, KHOZEMA HUSSAIN, MD, STELLA MADU, PA-C, NGOC DUONG, PA-C, DONNA WHITE, PHD, YUMEI CAO, MS, RAJNI MEHTA, MPH, HASHEM EL-SERAG, MD, MPH, STEVEN ASCH, MD, MPH, AND AMANDA MIDBOE, PHD

Cirrhosis-related morbidity and mortality is potentially preventable. Antiviral treatment in patients with cirrhosis-related to hepatitis C virus (HCV) or hepatitis B virus can prevent complications.[1-3] Beta-blockers and endoscopic treatments of esophageal varices are effective in primary prophylaxis of variceal hemorrhage.[4] Surveillance for hepatocellular cancer is associated with increased detection of early-stage cancer and improved survival.[5] However, many patients with cirrhosis are either not diagnosed in a primary care setting, or even when diagnosed, not seen or referred to specialty clinics to receive disease-specific care,[6] and thus remain at high risk for complications.

Our goal was to implement a population-based cirrhosis identification and management system (P-CIMS) to allow identification of all patients with potential cirrhosis in the health care system and to facilitate their linkage to specialty liver care. We describe the implementation of P-CIMS at a large Veterans Health Administration (VHA) hospital and present initial results about its impact on patient care.

P-CIMS Intervention

P-CIMS is a multicomponent intervention that includes a secure web-based tracking system, standardized communication templates, and care coordination protocols.

Web-based tracking system

An interdisciplinary team of clinicians, programmers, and informatics experts developed the P-CIMS software program by extending an existing comprehensive care tracking system.[7] The P-CIMS program (referred to as cirrhosis tracker) extracts information from VHA's national corporate data warehouse. VHA corporate data warehouse includes diagnosis codes, laboratory test results, vital status, and pharmacy data for each encounter in the VA since October 1999. We designed the cirrhosis tracker program to identify patients who had outpatient or inpatient encounters in the last 3 years with either at least 1 cirrhosis diagnosis (defined as any instance of previously validated International Classification of Diseases-9 and -10 codes)[8]; or possible cirrhosis (defined as either aspartate aminotransferase to platelet ratio index greater than 2.0 or Fibrosis-4 above 3.24 in patients with active HCV infection[9] [defined based on positive HCV RNA or genotype test results]).

The user interface of the cirrhosis

Content from this column was originally published in the "Practice Management: The Road Ahead" section of Clinical Gastroenterology and Hepatology (2018;16[4]:1182-6).

tracker is designed for easy patient lookup with live links to patient information extracted from the corporate data warehouse (recent laboratory test results, recent imaging studies, and appointments). The tracker also includes free-text fields that store follow-up information and alerting functions that remind the end user when to follow up with a patient. Supplementary Figure 1 (see https://doi.org/10.1016/j.cgh.2018.01.041) shows screen-shots from the program.

We refined the program through an iterative process to ensure accuracy and completeness of data. Each data element (e.g., cirrhosis diagnosis, laboratory tests, clinic appointments) was validated using the full electronic medical record as the reference standard; this process occurred over a period of 9 months. The program can run to update patient data on a daily basis.

Standardized communication templates and care coordination protocols

Our interdisciplinary team created chart review note templates for use in the VHA electronic medical record to verify diagnosis of cirrhosis and to facilitate accurate communication with primary care providers (PCPs) and other specialty clinicians. We also designed standard patient letters to communicate the recommendations with patients. We established protocols for initial clinical reviews, patient outreach, scheduling, and follow-ups. These care coordination protocols were modified in an iterative manner during the implementation phase of P-CIMS.

Setting and patients

Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston provides care to more than 111,000 veterans, including more than 3,800 patients with cirrhosis. At the time of P-CIMS implementation, there were three hepatologists and four advanced practice providers (APP) who provided liver-related care at the MEDVAMC.

The primary goal of the initial phase of implementation was to link patients with cirrhosis to regular liver-related care. Thus, the sample was limited to patients who did not have ongoing specialty care (i.e., no liver clinic visits in the last 6 months, including patients who were never seen in liver clinics).

Implementation strategy

We used implementation facilitation (IF), an evidence-based strategy, to implement P-CIMS.[10] The IF team included facilitators (F.K., D.S.), local champions (S.M., K.H.), and technical support personnel (e.g., tracker programmers). Core components of IF were leadership engagement, creation of and regular engagement with a local stakeholder group of clinicians, educational outreach to clinicians and support staff, and problem solving. The IF activities took part in two phases: preimplementation and implementation.

Preimplementation phase

We interviewed key stakeholders to identify facilitators and barriers to P-CIMS implementation. One of the implementation facilitators (F.K.) obtained facility and clinical section's leadership support, engaged key stakeholders, and devised a local implementation plan. Stakeholders included leadership in several disciplines: hepatology, infectious diseases, and primary care. We developed a map of clinical workflow processes to describe optimal integration of P-CIMS into existing workflow (Supplementary Figure 2; see https://doi.org/10.1016/j.cgh.2018.01.041).

Implementation phase

The facilitators met regularly (biweekly for the first year) with the stakeholder group including local champions and clinical staff. One of the facilitators (D.S.) served as the liaison between the P-CIMS team (F.K., A.M., R.M., T.T.) and the clinic staff to ensure that no patients were getting missed and to follow through on patient referrals to care. The programmers troubleshot technical issues that arose, and both facilitators worked with clinical staff to modify workflow as needed. At the start of IF, the facilitator conducted an initial round of trainings through in-person training or with the use of screen-sharing software. The impact of P-CIMS on patient care was tracked and feedback was provided to clinical staff on a quarterly basis.

Implementation results: Linkage to liver specialty care

P-CIMS was successfully imple-

Continued on page 29

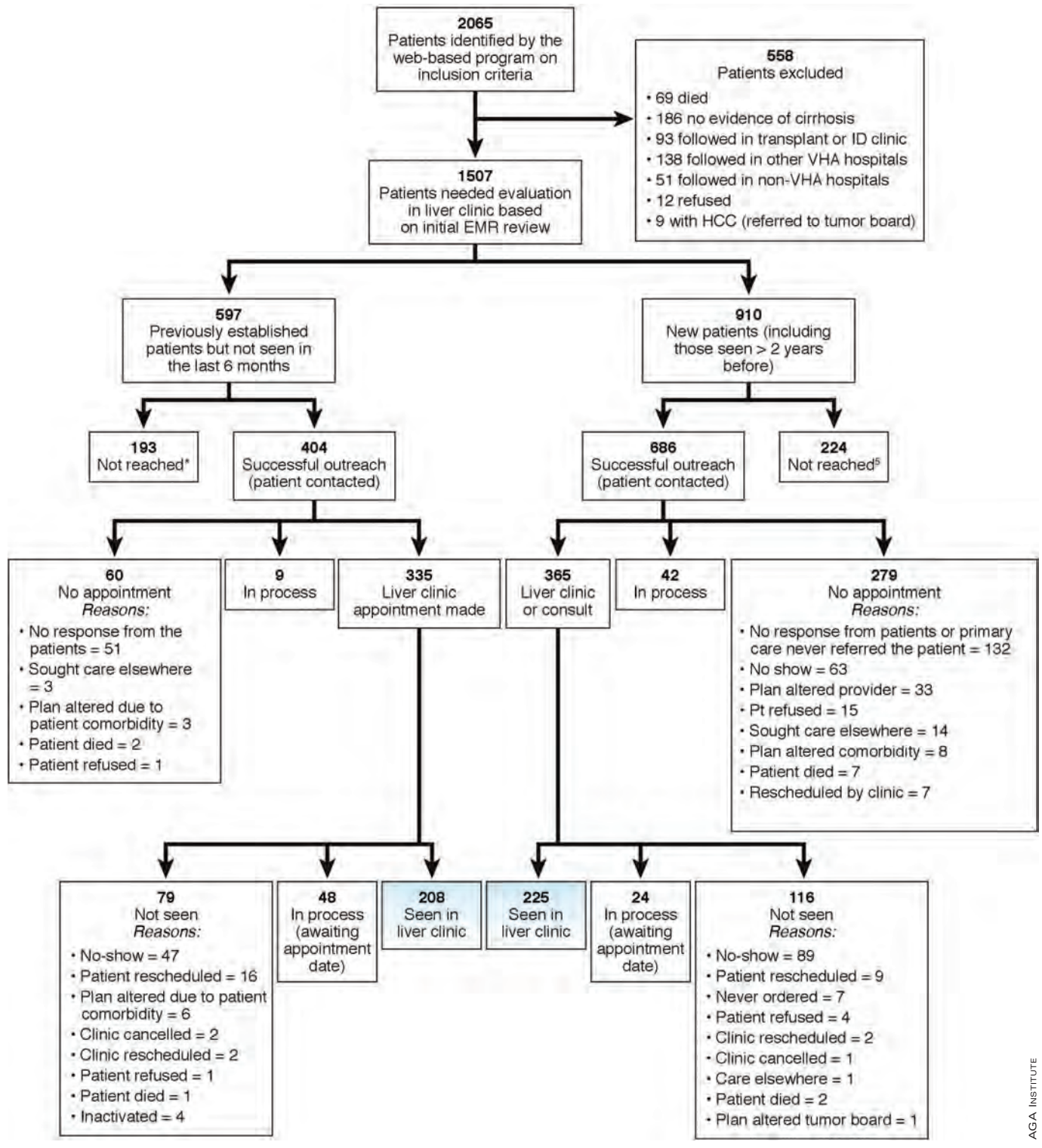

Figure 1. Initial results of P-CIMS implementation. Identification of patients with cirrhosis and their linkage to specialty care. EMR, electronic medical record; HCC, hepatocellular carcinoma.

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PROFESSIONAL OPPORTUNITIES

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mented at the MEDVAMC. Patient data were first extracted in October 2015 with five updates through March 2017. In total, four APP, one MD, and the facilitator used the cirrhosis tracker on a regular basis. The clinical team (APP) conducted the initial review, triage, and outreach. It took on average 7 minutes (range, 2–20 minutes) for the initial review and outreach. The APPs entered each follow-up reminder in the tracker. For example, if they negotiated a liver clinic appointment with the patient, then they entered a reminder to follow up with the date by which this step (patient seen in liver clinic) should be completed. The tracker has a built-in alerting function. The implementation team was notified (via the tracker) when these tasks were due to ensure timely receipt of recommended care processes.

We identified 2,065 patients who met the case definition of cirrhosis (diagnosed and potentially undiagnosed) and were not in regular liver care. Based on initial review, 1,507 patients had an indication to be seen in the liver clinic. Among the remaining 558, the most common reasons for not requiring liver clinic follow-up were: being seen in other facilities (138 in other VHA and 51 in outside hospitals), followed in other specialty clinics (e.g., liver transplant or infectious disease, n = 93), or absence of cirrhosis based on initial review (n = 165) (see Figure 1 for other reasons).

We used two different strategies to reach out to the patients. Of the 1,507 patients, 597 were previously seen in the liver clinics but were lost to follow-up. These patients were contacted directly by the liver clinic staff. The other 910 patients with cirrhosis (of 1,507) had never been seen in the ambulatory liver clinics (n = 559) or were seen more than 2 years before the implementation of cirrhosis tracker (n = 351). These patients were reached through their PCPs. We used standard electronic medical record templates to request PCP's assistance in reviewing patient's records and submitting a liver consultation after they discussed the need for liver evaluation with the patient.

Takeaway points

1. Cirrhosis patients without ongoing linkage to care can be identified through the electronic medical record (EMR) and linked successfully to liver specialty care.
2. Automated electronic patient tracking facilitates patient outreach, follow-up, and retention in care.
3. Support and commitment from national and local leadership as well as key stakeholders is critical for successful implementation of the automated electronic patient identification and management programs.

Of the 597 patients who were previously seen but lost to follow-up, we successfully contacted 404 (67.7%) patients via telephone and/or letters (for the latter, success was defined when patients called back); of these 335 (82.9%) patients had clinic appointments scheduled. In total, 208 (51.5% of 404; 34.8% of 597) patients were subsequently seen in the liver clinics during a median of 12-month follow-up. As shown in Figure 1, the most common reasons for inability to successfully link patients to the clinic were at the patient level, including no show, cancellation, and noninterest in seeking liver care. It took on average 1.5 attempts (range, 1–4) to link 214 patients to the liver clinic.

Of the other 910 patients with cirrhosis, 686 (75.4%) were successfully contacted; and of these 365 (53.2%) patients had liver clinic appointments scheduled. In total, 225 (61.7% of 365; 24.7% of 910) patients were seen in the liver clin-

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ics during a median of 12-month follow-up. The reasons underlying inability to link patients to liver specialty clinics are listed in Figure 1 and included shortfalls at the PCP and the patient levels. It took on average 2.4 attempts (range, 1–5) to link 225 patients to the liver clinic.

A total of 124 patients were initiated on direct-acting antiviral agents for HCV treatment and 18 new hepatocellular carcinoma cases were diagnosed as part of P-CIMS.

Discussion and future directions

We learned several lessons during this initiative. First, it was critical to allow time to iteratively revise the cirrhosis tracker program, with input from key stakeholders, including clinician end users. For example, based on feedback, the program was modified to exclude patients who had died or those who were seeking primary care at other VHA facilities.

Second, merely having a program that accurately identifies patients with cirrhosis is not the same as knowing how to get organizations and providers to use it. We found that it was critical to involve local leadership and key stakeholders in the preimplementation phase to foster active ownership of P-CIMS and to encourage the rise of natural champions. Additionally, we focused on integrating P-CIMS in the existing workflow. We also had to be cognizant of the needs of patients, such as potential problems with communication relating to notification and appointments for evaluation.

Third, several elements at the facility level played a key role in the successful implementation of P-CIMS, including the culture of the facility (commitment to quality improvement); leadership engagement; and perceived need for and relative priority of identifying and managing patients with cirrhosis, especially those with chronic HCV. We also had strong buy-in from the VHA National Program Office tasked with improving care for those with liver disease, which provided support for development of the cirrhosis tracker.

Overall, our early results show that about 30% of patients with cirrhosis without ongoing linkage to liver care were seen in the liver specialty clinics because of P-CIMS. This proportion should be interpreted in the context of the patient population and setting. Cirrhosis disproportionately affects vulnerable patients, including those who are impoverished, homeless, and with drug- and alcohol-related problems; a complex population who often have difficulty staying in care. Most patients in our sample had no linkage with specialty care. It is plausible that some patients with cirrhosis would have been seen in the liver clinics, regardless of P-CIMS. However, we expect this proportion would have been substantially lower than the 30% observed with P-CIMS.

We found several barriers to successful linkage and identified possible solutions. Our results suggest that a direct outreach to patients (without going through PCP) may result in fewer failures to linkage. In total, about 35% of patients who were contacted directly by the liver clinic met the endpoint compared with about 25% of patients who were contacted via their PCP. Future iterations of P-CIMS will rely on direct outreach for most patients. We also found that many patients were unable to keep scheduled appointments; some of this was because of inability to come on specific days and times. Open-access clinics may be one way to accommodate these high-risk patients. Although a full cost-effectiveness analysis is beyond the scope of this report, annual cost of maintaining P-CIMS was less than $100,000 (facilitator and programming support), which is equivalent to antiviral treatment cost of four to five HCV patients, suggesting that P-CIMS (with ability to reach out to hundreds of patients) may indeed be cost effective (if not cost saving).

In summary, we built and successfully implemented a population-based health management system with a structured care coordination strategy to facilitate identification and linkage to care of patients with cirrhosis. Our initial results suggest modest success in managing a complex population who often have difficulty staying in care. The next steps include comparing the rates of linkage to specialty care with rates in comparable facilities that did not use the tracker; broadening the scope to ensure patients are retained in care and receive guideline-concordant care over time. We will share these results in a subsequent manuscript. To our knowledge, cirrhosis tracker is the first informatics tool that leverages data from the electronic medical records with other tools and strategies to improve quality of cirrhosis care. We believe that the lessons that we learned can also help inform efforts to design programs that encourage use of administrative data–based risk screeners to identify patients with other chronic conditions who are at risk for suboptimal outcomes.

References

1. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9:509-16.
2. Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology. 2017;153:996-1005.
3. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med. 2004;351:1521-31.
4. Gluud LL, Klingenberg S, Nikolova D, et al. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. Am J Gastroenterol. 2007;102:2842-8.
5. Singal AG, Mittal S, Yerokun OA, et al. Hepatocellular carcinoma screening associated with early tumor detection and improved survival among patients with cirrhosis in the US. Am J Med. 2017;130:1099-106.
6. Kanwal F, Volk M, Singal A, et al. Improving quality of health care for patients with cirrhosis. Gastroenterology. 2014;147:1204-7.
7. Taddei T, Hunnibell L, DeLorenzo A, et al. EMR-linked cancer tracker facilitates lung and liver cancer care. J Clin Oncol. 2012;30:77.
8. Kramer JR, Davila JA, Miller ED, et al. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Aliment Pharmacol Ther. 2008;27:274-82.
9. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med. 2013;158:807-20.
10. Kirchner JE, Ritchie MJ, Pitcock

JA, et al. Outcomes of a partnered facilitation strategy to implement primary care-mental health. J Gen Intern Med. 2014;29:904-12.

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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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