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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

FRONTLINE MEDICAL NEWS

Dr. Thomas Imperiale reported findings from a large group of U.S. veterans who had at least one colonoscopy. View video at gihepnews.com.

Pull back on screening colonoscopy after nonadvanced adenomas

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – Evidence supports "backing off" from screening colonoscopies every 5 years for patients who had one or two nonadvanced adenomas removed during a prior colonoscopy, Thomas F. Imperiale, MD, AGAF, said at the World Congress of Gastroenterology at ACG 2017.

He reported findings from more than 66,000 U.S. veterans followed at any 1 of 13 Veterans Affairs medical centers for an average of more than 7 years. The 10,220 patients who underwent a second screening colonoscopy after an index colonoscopy that led to removal of one or two nonadvanced adenomas had 0.16% colorectal cancer mortality, compared with 0.13% among 8,718 patients with a similar history who did not receive follow-up colonoscopy. The rate of colorectal cancer death was 0.12% among 47,629 control veterans who had no adenomas removed during their index colonoscopy.

The differences among the three subgroups were not statistically significant

See **Colonoscopy** · *page 17*

Cardiopulmonary risk increased with intubation for upper GI bleed

BY ANDREW D. BOWSER
Frontline Medical News

Prophylactic endotracheal intubation (PEI) prior to endoscopy for upper GI bleeding in critically ill adults may actually increase, rather than decrease, the risk of unplanned cardiopulmonary events, according to results of a retrospective cohort study.

In particular, the study showed a significant increase in risk of patients developing pneumonia, according to study author Umar Hayat, MD, Medicine Institute, Cleveland Clinic, and colleagues.

"The practice of PEI could carry significant risks and might be a factor that leads to this dreaded outcome [pneumonia] in patients presenting with upper GI bleeding, instead of preventing it," Dr. Hayat and colleagues wrote (Gastrointest Endosc. 2017;86:500-9. doi: 10.1016/j.gie.2016.12.008).

The role of PEI in mitigating risk of cardiopulmonary adverse events remains controversial for patients presenting with upper GI bleeding, who can have mortality rates as high as 10% for nonvariceal bleeds and 20% for variceal causes, the

See **Intubation** · *page 4*

Biosimilars poised to save $54 billion

BY GREGORY TWACHTMAN
Frontline Medical News

Biosimilars could reduce overall spending on biologic products by $54 billion from 2017 to 2026, according to new research from the Rand Corp.

Given the level of uncertainty surrounding the biosimilars market, however, the range of savings could be as low at $24 billion or as high as $150 billion.

"Because of limited U.S. experience with biosimilars, the key assumptions on market share and biosimilar prices are 'best guesses' based on anecdotes or professional opinion," Andrew Mulcahy, PhD, a health policy researcher at Rand, and his colleagues, wrote in a perspective report.

There are currently three biosimilars on the market, including one product that

See **Biosimilars** · *page 19*

INSIDE

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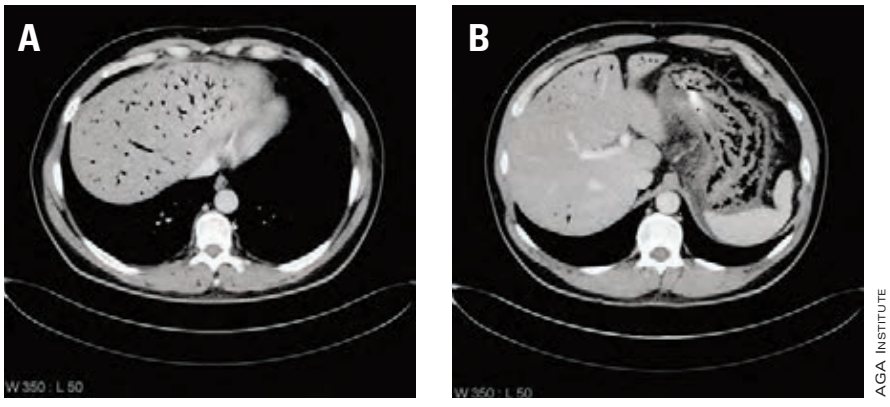
CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

By Mark C. Fok, BScPharm, Charles Zwirewich, MD, and Baljinder S. Salh, MBChB. Published previously in Gastroenterology (2013;144[3]:509, 658-9).

A 49-year-old man presented with severe epigastric pain and nonbloody emesis after ingestion of a naturopathic treatment for type 2 diabetes mellitus. He denied recent ingestion of nonsteroidal anti-inflammatory drugs and a prior history of chronic liver disease. In the emergency department, he was alert and orientated with a blood pressure of 140/84 mm Hg, a pulse rate of 80 beats per minute, and O_2 saturation of 97% on room air. On physical examination, he had moderate epigastric tenderness but without rebound, no abdominal distention, and normal bowel sounds. There were no localizing neurologic findings. Laboratory investigations revealed a white cell count of 11.4 x 10^9/L, a hemoglobin of 153 g/L, and a lactate level of 3.4 mmol/L.

Urgent abdominal computed tomography was performed, which revealed extensive portal venous gas throughout the liver (Figure A) and pneumatosis with thickening of the stomach wall (Figure B).



AGA Institute

What is your diagnosis and treatment?

The diagnosis is on page 9.

LETTER FROM THE EDITOR: Loss and liver coverage

DR. ALLEN

This month we learned of the passing of Dr. Marv Sleisenger (see his obituary on page 13 of this issue). There are few physicians who have had a greater impact on our field than Dr. Sleisenger. He was a consummate gentleman, enthusiastic teacher, great mentor, authored hundreds of research papers, and edited the most famous textbook of gastroenterology. Our thoughts and hearts are with his family and friends.

Articles in this month's issue cover some of the most difficult and vexing problems in gastroenterology. One article is a reminder to use colonoscopy resources wisely and back off surveillance intensity for some nonadvanced adenomas. Another highlights an issue that frustrates many of us – anesthesia's requirement to intubate UGI bleeds – and may not be the best practice. The third brings up the ongoing issue of biosimilars. Deeper in the issue we cover interesting findings about nonmedicine therapy for abdominal distention. Project ECHO is a tremendous demonstration of how changing our care delivery process can enhance patient care and maintain safe therapies. We cover an article on ERCP outcomes – linked to high volume (important for individual physicians and for centers where procedures are performed).

I would like to highlight our liver coverage. AASLD had their annual meeting in Washington in November. My colleague at University of Michigan (Dr. Anna Lok, AGAF) is the current president and helped spearhead a meeting that was packed with research and clinical information. We will be covering AASLD in greater depth in the months to come.

And while initial efforts to repeal the ACA have stalled, several key parts of the ACA continue to be modified or repealed either by executive orders or as part of the current tax reform efforts. We continue to view these efforts through the lens of our patients' access to care.

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

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FRONTLINE MEDICAL COMMUNICATIONS

GI & HEPATOLOGY NEWS is the official newspaper of the American Gastroenterological Association (AGA) Institute and provides the gastroenterologist with timely and relevant news and commentary about clinical developments and about the impact of health care policy. Content for **GI & HEPATOLOGY NEWS** is developed through a partnership of the newspaper's medical board of editors (Editor in Chief and Associate Editors), Frontline Medical Communications Inc. and the AGA Institute Staff. "News from the AGA" is provided exclusively by the AGA, AGA Institute, and AGA Research Foundation. All content is reviewed by the medical board of editors for accuracy, timeliness, and pertinence. To add clarity and context to important developments in the field, select content is reviewed by and commented on by external experts selected by the board of editors.

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The AGA Institute headquarters is located at 4930 Del Ray Avenue, Bethesda, MD 20814, ginews@gastro.org.

Editorial Offices 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

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References: 1. IMS Health, NPA Weekly, May 2017. **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; 2012. **4.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53.

HH13276BT-U May 2017

Shock, pneumonia more common

Intubation *from page 1*

investigators said.

Dr. Hayat and colleagues reviewed data for a total of 365 patients who had brisk upper GI bleeding, of whom 144 (39.5%) underwent PEI prior to esophagogastroduodenoscopy (EGD). The average patient age was 59 years, and 64% were male.

The composite primary endpoint of the study, cardiopulmonary unplanned events, was defined as occurrence of pneumonia, pulmonary edema, acute respiratory distress syndrome, shock/hypotension, arrhythmia, myocardial infarction, or cardiac arrest within 48 hours of EGD.

The final analysis included 200 intubated and nonintubated patients matched on a 1:1 basis using propensity score matching.

The researchers found that post-EGD adverse outcomes were more common in patients who had undergone PEI prior to EGD (odds ratio, 3.8; 95% confidence interval, 1.4-10.2), published data show. The rate of unplanned cardiopulmonary events was 20% for intubated patients, compared with 6% for nonintubated patients (P = .008).

Even after adjusting for the presence of esophageal varices, the difference remained significant, Dr. Hayat and colleagues wrote.

Pneumonia in particular was significantly more common in the PEI group: Published data show 14% of patients who underwent PEI had pneumonia within 48 hours of EGD, compared with 2% of nonintubated patients (P = .01).

'The benefits and risks of intubation should be carefully weighed when considering airway protection before an EGD in this group of patients.'

Rates of shock within 48 hours of EGD were also higher in the PEI group (14% vs. 6%), though the finding did not reach statistical significance, the authors added.

Currently, PEI is "variably used" in clinical practice, the authors wrote, and factors that may play into the decision to utilize this strategy include bleeding severity and ongoing hematemesis, among other factors. In survey data cited by Dr. Hayat and associates, 58% of experts said they would consider intubation for patients with ongoing hematemesis, and about one-quarter said they would intubate if they suspected hemodynamic compromise.

Although future prospective, controlled studies are needed to confirm these findings, the authors did advise caution in selecting patients for PEI in critically ill patients presenting with upper GI bleeding.

"The benefits and risks of intubation should be carefully weighed when considering airway protection before an EGD in this group of patients," they wrote.

The invesigators disclosed no financial relationships relevant to the current study.

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FROM THE AGA JOURNALS

Low tryptophan levels linked to IBD

BY AMY KARON
Frontline Medical News

Patients with inflammatory bowel disease (IBD) had significantly lower serum levels of the essential amino acid tryptophan than did healthy controls in a large study reported in the December issue of Gastroenterology (doi: 10.1053/j.gastro.2017.08.028).

Serum tryptophan levels also correlated inversely with both disease activity and C-reactive protein levels in patients with IBD, reported Susanna Nikolaus, MD, of University Hospital Schleswig-Holstein, Kiel, Germany, with her associates. "Tryptophan deficiency could contribute to development of IBD. Studies are needed to determine whether modification of intestinal tryptophan pathways affects [its] severity," they wrote.

Several small case series have reported low levels of tryptophan in IBD and other autoimmune disorders, the investigators noted. Removing tryptophan from the diet has been found to increase susceptibility to colitis in mice, and supplementing with tryptophan or some of its metabolites has the opposite effect. For this study, the researchers used high-performance liquid chromatography to quantify tryptophan levels in serum samples from 535 consecutive patients with IBD and 100 matched controls. They used mass spectrometry to measure metabolites of tryptophan, enzyme-linked immunosorbent assay to measure interleukin-22 (IL-22) levels, and 16S rDNA amplicon sequencing to correlate tryptophan levels with fecal microbiota species. Finally, they used real-time polymerase chain reaction to measure levels of mRNA encoding tryptophan metabolites in colonic biopsy specimens.

Serum tryptophan levels were significantly lower in patients with IBD than controls ($P = 5.3 \times 10^{-6}$). The difference was starker in patients with Crohn's disease ($P = 1.1 \times 10^{-10}$ vs. controls) compared with those with ulcerative colitis ($P = 2.8 \times 10^{-3}$ vs. controls), the investigators noted. Serum tryptophan levels also correlated inversely with disease activity in patients with Crohn's disease ($P = .01$), while patients with ulcerative colitis showed a similar but nonsignificant trend ($P = .07$). Low tryptophan levels were associated with marked, statistically significant increases in C-reactive protein levels in both Crohn's disease and ulcerative colitis. Tryptophan level also correlated inversely with leukocyte count, although the trend was less pronounced ($P = .04$).

IBD was associated with several aberrations in the tryptophan ky-

Continued on following page

FROM THE AGA JOURNALS

Continued from previous page

nurenine pathway, which is the primary means of catabolizing the amino acid. For example, compared with controls, patients with active IBD had significantly lower levels of mRNA encoding tryptophan 2,3-dioxygenase-2 (TDO2, a key enzyme in the kynurenine pathway) and solute carrier family 6 member 19 (SLC6A19, also called B0AT1, a neutral amino acid transporter). Patients with IBD also had significantly higher levels of indoleamine 2,3-dioxygenase 1 (IDO1), which catalyzes the initial, rate-limiting oxidation of tryptophan to kynurenine. Accordingly, patients with IBD had a significantly higher ratio of kynurenine to tryptophan than did controls, and this abnormality was associated with disease activity, especially in Crohn's disease ($P = .03$).

Patients with IBD who had relatively higher tryptophan levels also tended to have more diverse gut microbiota than did patients with lower serum tryptophan levels, although differences among groups were not statistically significant, the investigators said. Serum concentration of IL-22 also correlated with disease activity in patients with IBD, and infliximab responders had a "significant and sustained increase" of tryptophan levels over time, compared with nonresponders.

Potsdam dietary questionnaires found no link between disease activity and dietary consumption of tryptophan, the researchers said. Additionally, they found no links between serum tryptophan levels and age, smoking status, or disease complications, such as fistulae or abscess formation.

The investigators acknowledged grant support from the DFG Excellence Cluster "Inflammation at Interfaces" and BMBF e-med SYSINFLAME and H2020 SysCID. One coinvestigator reported employment by CONARIS Research Institute AG, which helps develop drugs with inflammatory indications. The other investigators had no conflicts of interest.

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In this interesting study, Nikolaus et al. found an association of decreased serum tryptophan in patients with inflammatory bowel disease (IBD), compared with control subjects. The authors also found an inverse correlation of serum tryptophan levels in patients with C-reactive protein in both ulcerative colitis and Crohn's disease and with active disease as defined by clinical disease activity scores in Crohn's disease. A validated food-frequency questionnaire found no difference in tryptophan consumption based on disease activity in a subset of patients, decreasing the likelihood that this association is secondary to altered dietary intake only and may be related to other mechanisms.

DR. HORST

An association of decreased serum tryptophan levels in IBD is very interesting and opens many avenues of research. It will be important to validate this relationship in the future with larger populations of IBD patients. Many of the exploratory analyses to further understand the mechanism behind this association, such as the relationship of serum tryptophan and microbiota diversity were done on a small number of patients and will need to be explored further. The effects of low tryptophan and ongoing inflammation may need to be characterized based on future endpoints such as endoscopic and/or histologic disease activity rather than just disease activity scores and/or CRP. Whether tryptophan deficiency is an effect of active disease or a contributor to the complex mechanism of mucosal inflammation is an important distinction to further understanding this pathway and its potential role as a biomarker or therapeutic target.

Sara Horst, MD, MPH, is an assistant professor, division of gastroenterology, hepatology & nutrition, Inflammatory Bowel Disease Center, Vanderbilt University Medical Center, Nashville, Tenn. She had no relevant conflicts of interest.

Biofeedback significantly improves abdominal distension

BY AMY KARON
Frontline Medical News

An electromyographic biofeedback program significantly improved abdominothoracic muscle control and abdominal distension compared with placebo in a randomized trial of patients fulfilling Rome III criteria for functional intestinal disorders.

Sensations of abdominal distension improved by 56% with biofeedback (standard deviation, 1%) versus 13% (SD, 8%) with placebo, wrote Elizabeth Barba, MD, of University Hospital Vall d'Hebron in Barcelona, and her associates. The study was published in the December issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.06.052). Biofeedback also led to a doubling of anterior wall muscle activity (101%; SD, 10%) compared with a 4% (SD, 2%) improvement with placebo. Finally, biofeedback lowered intercostal muscle activity by a mean of 45% (SD, 3%) compared with 5% (SD, 2%) with placebo (all P values less than .001).

"Biofeedback in this trial was applied using a complex technique that provided effective guidance to patients and allowed close control of the mechanistic effects of the intervention on postural tone," the researchers noted. "Having proved the [efficacy] of this treatment, the next steps are to develop and then to properly validate a simpler technique for widespread application."

Episodic abdominal distension is a primary reason for visiting gastroenterology clinics. Patients typically experience an objective, visible increase in girth with no detectable cause, although they often have irritable bowel syndrome, functional dyspepsia, or both. Past work has linked abdominal distension with increased diaphragmatic tone and ventral protrusion and decreased muscle tone of the abdominal wall, the researchers noted.

Therefore, they developed an electromyography (EMG) biofeedback program to help patients learn to correct abdominothoracic muscular dystony. The trial comprised 48 patients (47 women and 1 man) ranging in age from 21 to 74 years. During each 30-minute session, patients sat upright in a quiet room while EMG recorded the activity of the intercostal muscles, anterior abdominal wall (external oblique, upper rectus, lower rectus, and internal oblique muscles), and diaphragm. Patients reported their sensation of abdominal distension on a visual rating scale ranging from 0 (no distension) to 6 (extreme distension).

Those in the intervention group watched the EMG readout and were taught to reduce their intercostal and diaphragm activity while increasing the activity of the anterior abdominal muscles. Three training sessions occurred over 10 days and patients performed similar exercises at home for 5 minutes before each meal. Patients in the placebo group underwent the same instrumental interventions but did not watch the EMG recording, received no instructions about muscle control, and were given oral simethicone.

Symptoms associated with abdominal distension lessened by 57% (SD, 9%) in the biofeedback group and by 23% (4%) in the placebo group ($P = .02$). Treatment outcomes did not vary based on symptoms and there were no adverse effects of treatment, the researchers said. Furthermore, 19 patients in the placebo group who did not improve underwent biofeedback training and experienced benefits similar to those of the original intervention group. Sensations of abdominal distension and associated symptoms improved significantly immediately after biofeedback compared with baseline and continued to improve significantly over 6 months of follow-up.

The researchers acknowledged that the intervention program would need to be simplified before it could be deployed widely.

Funders included the Spanish Ministry of Economy and Competitiveness and the Instituto de Salud Carlos III. The researchers reported having no conflicts of interest.

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Project ECHO would cost-effectively expand HCV treatment

BY AMY KARON
Frontline Medical News

Training community health providers to treat chronic hepatitis C virus infection is a cost-effective way to expand treatment access and reduce the national burden of this condition, according to research published in the December issue of Gastroenterology (doi: 10.1053/j.gastro.2017.10.016).

"Our analysis demonstrates that fundamentally changing the care delivery model for HCV enables unparalleled reach, in contrast to simply using ever more cost-effective drugs in an inefficient system," wrote Thilo Rattay, MPH, of the University of Michigan School of Public Health, Ann Arbor, and his associates.

Dubbed Project ECHO (echo.unm.edu), it links multidisciplinary teams of specialists (hubs) to physicians and nurse practitioners in community practice (spokes). Each hub, which is usually based at an academic medical center, holds video conferences to teach providers about best practices for managing conditions ranging from autism to Zika virus infection. Initial reports suggest that Project ECHO can improve health care quality and access, the researchers noted.

Because patients with chronic HCV vastly outnumber gastroenterologists in the United States, Mr. Rattay and his coinvestigators used Markov models to evaluate Project ECHO's cost-effectiveness in the HCV setting. To do so, they created a decision tree and Markov models with Microsoft Excel, PrecisionTree, and @RISK by using data from the U.S. Census Bureau, MarketScan, and an extensive literature review.

The models yielded an incremental cost-effectiveness ratio of $10,351 per quality-adjusted life-year compared with the status quo, said the researchers. Cited willingness-to-pay thresholds are $50,000 and $100,000, indicating that Project ECHO is a cost-effective way to expand HCV treatment, they added. However, insurers would pay substantially more during the first 5 years of rollout – about $708 million versus $368 million with the status quo. During the first year, ECHO would cost payers about $350.5 million more than would the status quo, but 4,446 more patients would be treated, drastically reducing prevalence in the insurance pool. Consequently, subsequent costs would drop by nearly $11 million over the first 5 years of ECHO.

The investigators had no conflicts of interest.

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FROM THE AGA JOURNALS

High-volume endoscopy centers had better outcomes

BY AMY KARON
Frontline Medical News

Endoscopists who performed endoscopic retrograde cholangiopancreatography (ERCP) at high-volume centers had a 60% greater odds of procedure success compared with those at low-volume centers, according to the results of a systematic review and meta-analysis.

Watch this story's Video Insights at gastro.org/journals-and-publications/video-insights.

High-volume endoscopists also had a 30% lower odds of performing ERCP that led to adverse events such as pancreatitis, perforation, and bleeding, reported Rajesh N. Keswani, MD, MS, of Northwestern University, Chicago, and his associates. High-volume centers themselves also were associated with a significantly higher odds of successful ERCP (odds ratio, 2.0; 95% CI, 1.6-2.5), although they were not associated with a significantly lower risk of adverse events, the reviewers wrote. The study was published in the December issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.06.002).

Diagnostic ERCP has fallen 7-fold in the past 30 years while therapeutic use has increased 30-fold, the researchers noted. Therapeutic use spans several complex pancreaticobiliary conditions, including chronic pancreatitis, malignant jaundice, and complications of liver transplantation. This shift has naturally increased the complexity of ERCP, the need for expert endoscopy, and the potential risk of adverse events.

Therefore, the reviewers searched MEDLINE, EMBASE, and the Cochrane register of controlled trials for prospective and retrospective studies published through January 2017. In all, the researchers identified 13 studies that stratified outcomes by volume per endoscopist or center. These studies comprised 59,437 procedures and patients. Definitions of low volume varied by study, ranging from less than 25 to less than 156 annual ERCPs per endoscopist and from less than 87 to less than 200 annual ERCPs per center. Endoscopists who achieved this threshold were significantly more likely to perform successful ERCPs than were low-volume endoscopists (OR, 1.6; 95% CI, 1.2-2.1), and were significantly less likely to have patients develop pancreatitis, perforation, or bleeding after ERCP (OR, 0.7; 95% CI, 0.5-0.8).

One reviewer acknowledged support from the University of Colorado Department of Medicine Outstanding Early-Career Faculty Program. The reviewers reported having no relevant conflicts of interest.

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The field is shifting toward performance of complex ERCPs by those who have had advanced training. Consistent with this, the meta-analysis by Keswani et al. highlights benefits of higher-volume centers and endoscopists – improved ERCP success rate (at the provider and practice level) and reduced adverse events (provider level only).


DR. KETWAROO

Consolidating performance of ERCPs at fewer high-volume centers presents its own obstacles, including potentially limiting access to care. And, as the authors point out, lower volume is not necessarily the cause of worse outcomes. Indeed, it is not known if lower-volume endoscopists would do better at higher-volume centers – i.e., is it the infrastructure, including technicians and equipment as well as the consistent performance of ERCPs, that are the main drivers of improved outcomes?

Overall, this large, well-performed meta-analysis adds to the growing chorus that endoscopists and endoscopic centers will have better results if the endoscopists are specially trained and routinely perform these procedures. Future studies are needed to more accurately define procedure success and assess other variables that affect outcomes for which volume may only be a proxy. In an era of reporting and demonstrating value in endoscopic care, quality metrics for ERCP performance may not be fully appreciated but eventually may become the driving force in consolidation of these procedures to particular centers or providers, regardless of volume.

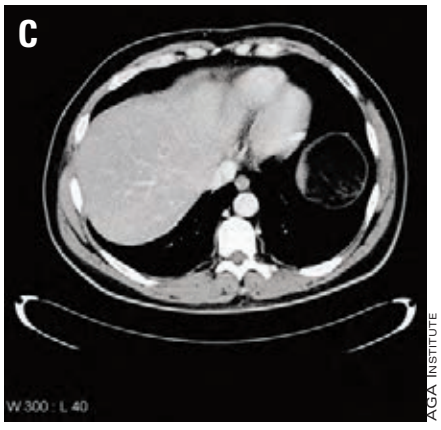
G. Avinash Ketwaroo, MD, MSc, is assistant professor in the division of gastroenterology and hepatology at Baylor College of Medicine, Houston, and an associate editor of GI & Hepatology News. He has no conflicts of interest.

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" on page 2: Hydrogen peroxide ingestion causing significant portal venous gas and stomach wall thickening

Upon further questioning, it was found that the patient accidentally ingested approximately 50 mL of concentrated 35% hydrogen peroxide (H_2O_2), which he was using in diluted form as a naturopathic treatment for his diabetes mellitus. He was admitted to our institution and closely monitored for evidence of perforation and respiratory distress. Given the extent of portal venous gas, he was promptly treated with hyperbaric oxygen to prevent cerebral gas embolism. He remained stable over the next 24 hours and repeat imaging the next day revealed dramatic improvement of the portal venous gas (Figure C). He was discharged on day 4 of hospitalization with no obvious clinical sequelae. Outpatient gastroscopy was arranged to assess any further damage, but he was lost to follow-up.



H_2O_2 is a common naturopathic remedy that is claimed to treat an array of conditions from diabetes mellitus, to cancer, to HIV.[1] Concentrations vary from 3% solutions found in disinfectants to 35% solutions found in health food stores. Injury is thought to occur via three mechanisms: caustic injury, oxygen gas formation, and lipid peroxidation.[1] Treatment is primarily supportive as H_2O_2 rapidly decomposes to water and oxygen gas. Because of the risk of cerebral gas embolism, 100% oxygen or hyperbaric oxygen therapy has been suggested to prevent brain infarction.[2] A review of hyperbaric oxygen in 11 cases of portal venous gas from H_2O_2, comprising accidental ingestion in 10 and therapeutic misadventure in 1, found it successfully resolved all portal gas in 9 patients and nearly all in 2. Concentrations of H_2O_2 were 35% in 10 patients and 12% in 1. Time to hyperbaric oxygen ranged from 2 to 6.5 hours. Ten patients were discharged within 1 day, and 1 patient at 3.5 days.[2] Endoscopy is suggested for persistent hematemesis, intractable vomiting, or significant oral burns.[1] However, because of the rarity of this condition, the diffuse nature of tissue injury, and the usually favorable outcome after hyperbaric oxygen, the precise role of this intervention remains undefined.

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ginews@gastro.org

Closing the colonoscopy loophole

AGA applauds Shazia Mehmood Siddique, MD, for her recent op-ed in the Philadelphia Inquirer that sheds light on the "colonoscopy loophole."

What is the colonoscopy loophole?

The Affordable Care Act covers screening colonoscopies at no cost to patients as long as no polyps are found. As Dr. Siddique explains in her article, finding a polyp changes the billing code to a therapeutic colonoscopy, a reclassification that changes the procedure from a diagnostic screening to an intervention. And this means a bill is generated. This reclassification directly affects those covered by Medicare and not commercial insurers.

AGA leaders urge Congress to correct this problem

Dr. Siddique – a member of the AGA Trainee and Early Career Committee and AGA Clinical Guidelines Committee – joined other AGA leaders for AGA Advocacy Day in late September where they spoke directly to lawmakers about patients who are blindsided by this regulation. AGA supports closing this loophole to ensure patients continue to have access to quality care and preventative screenings. We encourage all members to continue to share their patient stories, like Dr. Siddique has, to help raise awareness of this issue.

AGA can help you advocate for GI

Watch an AGA webinar at www.gastro.org/webinars/CongressionalMeeting (login required) to learn more about how to set up congressional meetings in your district, or contact Navneet Buttar, AGA government and political affairs manager, at nbuttar@gastro.org or 240-482-3221.

ginews@gastro.org

AGA launches new registry to track patient outcomes

The AGA Center for GI Innovation and Technology is excited to announce a new clinical research registry to track and evaluate patient outcomes after trans-oral endoscopic suturing procedures.

The Prospective Registry for Trans-Oral Suturing Applications ("Endoscopic Suturing Registry") will collect real-world data related to the safety and effectiveness of procedures done with Apollo Endosurgery's OverStitch™ Endoscopic Suturing System. Jennifer Maranki, MD, director of endoscopy, Penn State Milton S. Hershey School of Medicine, and Brian Dunkin, MD, head of endoscopic surgery and medical director, Houston Methodist Institute for Technology, Innovation and Education, will serve as principal investigators for the Endoscopic Suturing Registry. The Registry will begin collecting patient data in early 2018.

We asked Michael Kochman, MD, AGAF, past chair of the AGA Center for GI Innovation and Technology and director of the Center for Endoscopic Innovation, Research and Training at the University of Pennsylvania, to weigh in on the value of this new registry.

"Flexible endoscopic suturing is an important tool for the treatment of a number of GI disorders. As these procedures become more routine in GI and surgery practices across the country, the real-world data AGA will collect through the Endoscopic Suturing Registry will guide all stakeholders in making informed decisions around the continued adoption of these procedures in clinical practice."

Learn more about AGA's registry initiative at www.gastro.org/patient-care/registries-studies.

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DDSEPeight Quick quiz

Digestive Diseases Self-Education Program

Q1: Which of the following conditions is associated with smooth muscle atrophy impairing esophageal clearance, contributing to prolonged esophageal acid contact and reflux esophagitis?
A. Diabetes mellitus
B. Polymyositis
C. Mixed connective tissue disease
D. Lichen planus
E. Barrett's esophagus

Q2: A 55-year-old man was diagnosed with a 3.1-cm cyst in the tail of the pancreas 2 years ago. He had an endoscopic ultrasound–guided fine-needle aspiration at that time and approximately 2 cc of mucinous fluid were aspirated; cyst fluid CEA (carcinoembryonic antigen) was 790 ng/mL and cytology showed a paucicellular specimen with abundant extracellular mucin. The patient was asymptomatic and opted for radiologic surveillance with MRI. On his most recent MRI, the cyst size is currently 3.4 cm. In addition, the MRI notes the presence of an enhancing nodule in the wall of the cyst measuring 5 mm and the pancreatic duct in the tail is mildly dilated to 5 mm. He continues to be asymptomatic and in good health.

What is the most appropriate next step in the management of this patient?
A. Repeat MRI in 3 months for surveillance
B. Repeat MRI in 6 months for surveillance
C. Endoscopic ultrasound–guided fine-needle aspiration (EUS with FNA)
D. Endoscopic retrograde cholangiopancreatography (ERCP) with brushings
E. Distal pancreatectomy

The answers are on page 13.

GIs should be able to prescribe the most beneficial treatments

Appealing step therapy protocols can be time consuming and burdensome for physicians and patients, and can takes months to resolve. The Restoring the Patient's Voice Act (HR 2077), introduced by physicians Reps. Brad Wenstrup, R-OH, and Raul Ruiz, D-CA, would provide a clear and timely appeals process when a patient has been subjected to step therapy by their insurance provider.

AGA endorsed this legislation to provide patients with a clear, equitable and fair appeals process when subjected to step therapy protocols. Step therapy, also known as "fail first," requires patients to try and fail medications by insurers before being covered by the initial therapy prescribed by their health care provider. This practice jeopardizes the physician-patient relationship, since it bypasses what the physician believes is the best treatment for their patient. Although step therapy is used by insurers as a cost-containment mechanism, it has been shown to not save money in the long run due to complications that patients suffer, which can require additional physician visits, emergency department visits or even costly hospitalizations. With the increase of biologics to treat diseases like inflammatory bowel disease (IBD), more and more patients with digestive diseases are subject to this policy.

HR 2077 would require employer-sponsored health plans to:

- Establish a clear and convenient process for physicians to appeal a step therapy protocol for their patient.
- Grant patients exceptions to step therapy under five critical circumstances.
- Expedite care by requiring a timely decision for appeals — three days or 72 hours, or within 24 hours, if life threatening.

AGA is working with patient advocacy groups, like the Crohn's and Colitis Foundation, provider and professional societies to educate members of Congress on this issue and the implications it has for patients being able to access the right treatment at the right time. We will continue to work with other stakeholders in garnering support for this critical legislation that will restore the physician-patient relationship.

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Giving new hope to IBD patients and more options to physicians.

BEST HOSPITALS U.S.News & WORLD REPORT HONOR ROLL 2017-18

The team at the UPMC Inflammatory Bowel Disease (IBD) Center has developed a new way to connect our leading IBD program with more than a dozen other top programs around the country. *IBD Live* is a first-of-its-kind interactive video and publication series focused exclusively on sharing information about inflammatory bowel diseases. *IBD Live* allows multiple centers to actively participate at the same time, which facilitates consistency in IBD care, the sharing of research, and an immediate exchange of treatment options for real patient cases. The conference proceedings also are published in the journal *Inflammatory Bowel Diseases* and fulfill CME accreditation. To learn more, visit **UPMCPhysicianResources.com/Gastro**.

UPMC LIFE CHANGING MEDICINE

UPMC Presbyterian Shadyside is ranked among America's Best Hospitals by *U.S. News & World Report.*

A letter from Robert S. Sandler, MD, MPH, AGAF

Dear Colleagues,

I ask you, as AGA Research Foundation Chair, where would clinical practice be today without GI research?

The way we diagnose and treat patients is thanks to years of research. But as you know, federal research funding is at risk. Promising, early-stage investigators find it increasingly difficult to secure funding and many leave the field because they are unable to sustain a research career.

This is bad news for digestive health patients and the clinicians who care for them.

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

At a time when we are on the brink of major scientific breakthroughs, there is a growing gap in federal funding for research. Many well-qualified young investigators cannot get government funding. Gifts to the AGA Research Foundation this year directly supported 52 talented investigators. Despite this success, over 200 other innovative and promising research ideas went unfunded.

I am asking you to support a cause important to me and equally important to you. You can help fill the funding gap and protect the next generation of investigators by joining me in supporting the AGA Research Foundation through a personal gift.

Every dollar is a step forward ... to new treatments. To cures impacting patients' lives. To new generations of talented investigators in digestive disease research.

Please help us continue our efforts by making your tax-deductible donation. Donate today at www.gastro.org/donateonline3.

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

Three easy ways to give

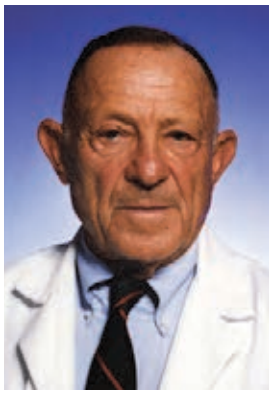
Online: www.gastro.org/donateonline3
Through the mail:
AGA Research Foundation
4930 Del Ray Avenue
Bethesda, MD 20814
Over the phone: 301-222-4002

All gifts are tax-deductible to the fullest extent of U.S. law.

AGA remembers former AGA President Marvin Sleisenger, MD, AGAF

Marvin H. Sleisenger, MD, AGAF, of Kentfield, Calif., died at age 93 on Thursday, Oct. 19, 2017. Dr. Sleisenger served as editor of *Gastroenterology* from 1965 to 1970, and as president of AGA in 1976.

Dr. Sleisenger attended Harvard College and Harvard Medical School. He trained at Harvard, the University of Pennsylvania, and Cornell Medical School. During the Korean War, he served in the U.S. Naval Medical Corps. He was a member of the faculty at Cornell Medical School and in 1954 was appointed as chief of the division of gastroenterology. In 1968, he became professor and vice chairman of the department of medicine of the University of California, San Francisco and chief of the medical service at the Veterans Administration Hospital. His achievements as an outstanding educator were recognized in 1994 when he became the recipient of the AGA Distinguished Educator Award.


DR. SLEISENGER

In 1989, Dr. Sleisenger received the Julius Friedenwald Medal, recognizing his significant contributions to AGA and the field of gastroenterology, which includes founding and co-editing 10 editions of Gastrointestinal and Liver Disease — widely regarded as the leading textbook in the field — with John Fordtran, MD, AGAF. Dr. Sleisenger and his wife also contributed to the field as proud AGA Legacy Society members.

Dr. Sleisenger's full obituary was published in the SFGate. Members, colleagues, and friends posted remembrances in the Community.

Memorial services were held on Sunday, Oct. 29, 2017, at 11 a.m., at the Chapel of the Mt. Tamalpais Cemetery, 2500 Fifth Avenue, San Rafael, Calif.

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AGA's investment in the future of GI

What will the practice of gastroenterology look like in 20 years? It is our hope that physicians will have an abundance of new tools and treatments to care for their patients suffering from digestive disorders.

How will we get there? New treatments and devices are the result of years of research.

To help make this dream a reality, AGA – through the AGA Research Foundation – has made a commitment to support investigators in GI and hepatology with its Research Awards Program. In the past year, the foundation provided $2.2 million in research funding to 52 highly qualified investigators. These diverse researchers range from young investigators to more seasoned leaders in GI, all embarking on novel research projects that will advance our understanding of digestive conditions and pave the way for future discoveries in the field.

A snapshot of the foundation's impact this year is highlighted in the chart below. The AGA Research Foundation sincerely thanks all of its donors – without your gifts, this work wouldn't be possible. Please join us in advancing GI research with a tax-deductible gift to the AGA Research Foundation at www.gastro.org/about/aga-research-foundation.

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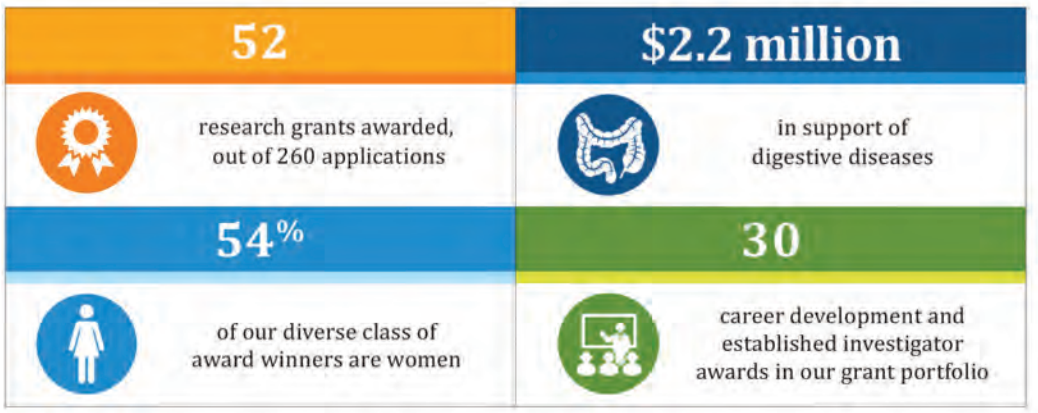

Travel awards available

DDW will award up to 20 young investigators with the Basic Science Travel Award. Selected authors of basic science abstracts will receive a $1,000 travel grant along with recognition at a reception during DDW 2017. Residents and fellows are encouraged to apply.

The AGA Research Foundation also offers various travel awards:

- AGA-GRG Fellow Abstract Award
- AGA-Moti L. & Kamla Rustgi International Travel Awards
- AGA Student Abstract Award

For more information on travel awards and other DDW-related grants, please visit the DDW website, www.ddw.org.

DDSEPeight
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Correct Answer: C

Rationale

Mixed connective tissue disease can be associated with atrophy of the smooth muscle of the gut, like scleroderma. In the esophagus, this can manifest as a hypotensive lower esophageal sphincter and impaired esophageal smooth muscle peristalsis; in extreme cases, there is absent contractility in the esophagus. This contributes to impaired esophageal clearance of refluxed material, leading to prolonged acid residence times in the esophagus and severe reflux esophagitis. Many patients with mixed connective tissue disease have overlap Sjogren's syndrome, reducing salivary neutralization of esophageal mucosal acidification and further contributing to esophagitis. While esophageal body motor function can be suboptimal in diabetes mellitus and Barrett's esophagus, the mechanism of hypomotility is not smooth muscle atrophy and fibrosis. Polymyositis can affect skeletal muscle of the proximal esophagus, but not the smooth muscle. Lichen planus affects mucosa but not muscle.

Reference

1. Savarino E., Mei F., Parodi A., et al. Gastrointestinal motility disorder assessment in systemic sclerosis. Rheumatology (Oxford). 2013 Jun;52(6):1095-100.
2. Langdon P.C., Mulcahy K., Shepherd K.L., et al. Pharyngeal dysphagia in inflammatory muscle diseases resulting from impaired suprahyoid musculature. Dysphagia. 2012 Sep;27(3):408-17.

Q2. Correct Answer: E

Rationale

On serial imaging, two worrisome features have developed in the pancreas cyst, i.e., an enhancing mural nodule and dilation of the main pancreatic duct. These features are high-risk stigmata, and therefore surgical resection is recommended. EUS FNA can be considered but is unlikely to change management if cytology is negative. Radiologic surveillance is not appropriate unless the patient refuses surgery.

Reference

1. Tanaka M., Fernández-del Castillo C., Adsay V., et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183-97.

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Survey colonoscopy outpatients to flag high cancer risk

BY BIANCA NOGRADY
Frontline Medical News

'Our results using both electronic and paper-based tools demonstrate that collection and review of family history information is feasible in the outpatient colonoscopy setting and provides physicians with information for CRC risk assessment that is immediately relevant to patient care.'

Point-of-care surveys on family history of colorectal cancer for individuals undergoing colonoscopy can identify people who would benefit from genetic evaluation, a study showed.

The feasibility and performance of two survey methods – one paper and one electronic – were evaluated to identify individuals at high genetic risk of colorectal cancer.

"Multiple studies have shown that family history assessments performed in primary care and in oncology and gastroenterology clinical settings are incomplete or inaccurate," wrote Tannaz Guivatchian, MD, of the department of internal medicine at the University of Michigan Hospital, Ann Arbor, and coauthors. "There remains a need for targeted family history assessments to screen patients for hereditary cancer syndromes at point-of-care cancer screenings, such as colonoscopy."

In the first cohort of the current study, a five-question paper survey was given to 600 patients after they had checked in for their colonoscopy, and the results were immediately given to the endoscopist performing the procedure. The second cohort of 100 patients took the paper survey and a more comprehensive tablet-based electronic survey (Gastrointest Endosc. 2017;86[4]:684-91).

The paper survey alone identified 60 colonoscopy patients (10%) as high risk because they met at least 1 of the 10 genetic referral criteria. The retrospective chart review 60 days after the procedure showed that 32 patients (5.3%) were referred for genetic evaluation, 31 of whom met at least 1 of the 10 criteria for referral.

Continued on following page

Minimize harm from surveillance

Colonoscopy *from page 1*

after adjustment for baseline differences in age, sex, race, number of comorbidities, and tobacco use, said Dr. Imperiale, a gastroenterologist and professor of medicine at Indiana University, Indianapolis.

In current U.S. practice, many gastroenterologists perform follow-up colonoscopy about 5 years after removing one or two nonadvanced adenomas during a screening colonoscopy, Dr. Imperiale said during a video interview. Deferring follow-up colonoscopy in the absence of any clinical indication seems advisable, he said, especially for older patients with two or more comorbidities who had a high-quality index colonoscopy with good preparation and good colonic visibility.

An extended interval before repeat surveillance seems particularly appropriate for patients with a higher risk for adverse effects from the colonoscopy preparation.

"We just can't do colonoscopy for surveillance on this subgroup continuously; it doesn't make sense," he said.

No randomized trial results have documented the need for stepped up colonoscopies in patients with a history of one or two nonadvanced adenomas, and these new observational findings are consistent with prior observational reports.

"These data need to be integrated with common sense," he said. An extended interval before repeat surveillance seems particularly appropriate for patients with a higher risk for adverse effects from the colonoscopy preparation and for patients more likely to die from a cause other than colorectal cancer.

Backing off on repeat colonoscopy "minimizes the harm from surveillance. As patients get older they don't tolerate the prep as well. It grows more onerous, and the returns diminish," Dr. Imperiale said.

The patients included in the review had their index colonoscopy performed during 2002-2009, when they averaged about 61 years old, and about 95% were men. Their average Charlson comorbidity index was about 1.3. The incidence of colorectal cancer during follow-up after the index colonoscopy was 0.18% in patients with one or two nonadvanced adenomas in their index examination and no follow-up colonoscopy, 0.71% in those with nonadvanced adenomas who had one or more subsequent colonoscopies, and 0.31% in the people with no adenomas removed during the index procedure.

The rates of all-cause death during follow-up of the three subgroups were notably different: 34% in those with nonadvanced adenomas and no repeat colonoscopy, 13% in patients with nonadvanced adenomas and repeat colonoscopy, and 21% in those without nonadvanced adenomas. Dr. Imperiale discounted the significance of comparing rates of all-cause mortality, stressing that the most relevant primary endpoint is colorectal cancer mortality.

Dr. Imperiale reported having no disclosures.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

Nivolumab may extend survival in HCC patients

BY RICHARD MARK KIRKNER
Frontline Medical News

WASHINGTON – A multinational clinical trial has found that the metastatic cancer agent nivolumab can improve long-term survival and durable tumor responses in patients with advanced hepatocellular carcinoma (HCC) whether or not they've had previous treatment with a chemotherapy agent already approved for advanced primary liver cancer, a principal investigator reported at the annual meeting of the American Association for the Study of Liver Diseases.

"Nivolumab has demonstrated clinically meaningful efficacy across etiologies in sorafenib-naive and -experienced patients with extended follow-up," Bruno Sangro, MD, of the University of Navarra in Pamplona, Spain, said in reporting results of the CheckMate-040 trial. "The median overall survival is 15 and 15.6 months in patients who were sorafenib experienced in both the dose-escalation and expansion cohorts."

The dose-escalation cohort received 0.1 to 10 mg/kg of nivolumab (Opdivo) while the dose-expansion group received a steady dose of 3 mg/kg. In all, 262 patients participated in the trial, 80 of whom had never been on sorafenib (Nexavar) therapy. The survival outcome in these subgroups, Dr. Sangro said, "really speaks for the consistency and the robustness of the results."

Trial participants had inoperable, usually metastatic HCC, with Child-Pugh scores up to and including 7 in the escalation group or up to and including 6 in the expansion group. Their aspartate aminotransferase and alanine aminotransferase scores were in the upper limits of normal, and bilirubin was less than or equal to 3 mg/dL. If they had hepatitis B virus (HBV), their viral load had to be less than 100 IU/mL and they had to be on effective antiviral therapy. Any history of hepatic encephalopathy or clinically significant ascites and an active HBV and hepatitis C (HCV) coinfection were grounds for exclusion.

"Most patients had to discontinue nivolumab because of disease progression," Dr. Sangro noted, so that only 36 patients, or 14%, were continuing treatment at the time of this analysis. Thirteen patients in the total population that discontinued nivolumab did so because of toxicity, he said.

"Around 20% of patients achieved an objective remission that included complete responses in all subgroups of patients; 15% of progressors and 23% of sorafenib-intolerant patients had an objective response," Dr. Sangro said. In terms of overall response, about half of all patients in the sorafenib-experienced subgroups had a complete or partial response or stable disease: 51% in the dose-escalation subgroup and 54% in the dose-expansion subgroup.

Although tumor responses were associated with declines in alpha-fetoprotein levels, "it's unlikely that these biomarkers will be useful either for monitoring or selecting patients for treatment," he added. "Indeed, baseline alpha-fetoprotein levels were comparable between responders and nonresponders to nivolumab" Dr. Sangro said.

"We also showed there was some impact on HCV viral kinetics in infected individuals," Dr. Sangro noted. "The overall safety profile for the HCC population is consistent with other tumor types in which nivolumab is approved; these include patients who are infected with hepatitis B or C viruses."


COURTESY BRUNO SANGRO, MD
Dr. Bruno Sangro said that nivolumab has demonstrated clinically meaningful efficacy.

The study showed that 36% (19/53) of HCV infected patients had a greater than 1-log decrease in viral load. No signs of additional antiviral activity were detected among HBV-infected patients already on effective antiviral treatment: only 5% (3/59) posted a up to 1-log decrease in HB surface antigen levels, and 11% (7/64) of patients had increases in viral load. "These increases occurred in the setting of low-level viremia." Dr. Sangro said. "They were asymptomatic and [nivolumab] did not result in changes in hepatic parameters or other serious adverse events."

With regard to adverse events, 77% of all patients had some treatment-related adverse events, ranging from fatigue to rash to dry mouth to increased lab levels, but only 20% were grade 3 or 4, and 88% of those resolved in an average of 8 weeks, Dr. Sangro said.

More research into nivolumab for HCC is needed, Dr. Sangro said. "Ongoing and future studies in patients with advanced tumors will evaluate nivolumab in the first-line setting or in combination with other agents," he said.

Dr. Sangro disclosed relationships with Bayer Schering Pharma, Onxeo, Astra Zeneca, and Bristol-Myers Squibb. Bristol-Myers Squibb funded the trial, and Chrysalis Medical Communications assisted in reporting the study results.

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Continued from previous page

Of the patients picked up by the paper survey, 21 (35%) had documentation of a genetic evaluation. Seven of these had germline mutations that predisposed them to cancer, 10 had undergone genetic testing that did not find any pathogenic mutations, and 4 did not undergo genetic testing; 3 were lost to follow-up and 1 was in hospice.

The research team also sought feedback from 21 endoscopists about the paper survey. The majority (85%) found the risk assessment tool helpful, with nearly three-quarters of them (71%) saying that it influenced their surveillance recommendations and 28.5% saying it prompted them to refer the patient for genetic evaluation.

In the second cohort, 9 of the 100 patients were found to be high risk by meeting at least 1 of the 10 criteria on the paper survey and/or achieving a PREMM1,2,6 score – a tool for assessing the likelihood of mutations associated with Lynch syndrome – of 5% or higher.

Of these nine patients, six were flagged for genetic evaluation based on the results of the paper survey, and three were picked up by the electronic survey. Three were referred for genetic evaluation.

An additional patient was also flagged for genetic evaluation after a review of the patient's electronic medical record picked up information that the patient did not provide in either the paper or electronic survey.

In this second phase of the study, researchers found that only 73% of the patients approached were able to successfully complete the electronic survey before their procedure. The team had also mailed letters to 500 patients who invited them to complete the electronic survey at home before their colonoscopy appointment, but only two patients did so.

"Although several family history surveys and CRC [colorectal cancer] risk assessment tools have been published in the literature, operationalizing cancer risk assessments in busy clinical settings has been a consistent barrier to implementation," the authors wrote. "Our results using both electronic and paper-based tools demonstrate that collection and review of family history information is feasible in the outpatient colonoscopy setting and provides physicians with information for CRC risk assessment that, is immediately relevant to patient care."

The authors stressed that while the short paper survey could be filled out quickly and had a near 100% completion rate, the more comprehensive electronic survey provided a more detailed family cancer history, which would help clinicians identify patients needing genetic evaluation.

They also pointed out that each survey method identified patients not picked up by the other method.

The study was supported by the National Cancer Institute. No conflicts of interest were declared.

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Several variables at play

Biosimilars *from page 1*

is biosimilar to filgrastim and two that are biosimilar to infliximab. Two other biosimilar products, one for adalimumab and one for etanercept, have received approval from the Food and Drug Administration, but neither is available for sale yet.

"Whether actual cost savings end up above or below our baseline estimate hinges in large part on whether manufacturers continue to have a business case to invest in developing and marketing biosimilars," the authors noted, citing a number of areas, including intellectual property litigation, payment, price competition, nonprice competition from reference biologic manufacturers, naming convention, and interchangeability.

Getting over these hurdles could require legislative or regulatory solutions.

"The pervasive uncertainty in the U.S. biosimilar market – including questions as to whether the market will be sustainable and lead to cost savings, as intended – presents two choices for policy makers," Dr. Mulcahy and his colleagues wrote. "One strategy is to let the market continue to develop under current policies."

The alternative could be policy levers to "help steer the U.S. biosimilar market more quickly to a sustainable, competitive state," they continued. "For example, regulators at the FDA could experiment with new approaches to provide stronger, earlier signals through guidance documents or other mechanisms on expectations surrounding interchangeability and other topics."

The FDA appears to be moving on the latter. In an Oct. 23 blog post, FDA Commissioner Scott Gottlieb, MD, and Leah Christl, PhD, associate director for therapeutic biologics in the office of new drugs at the FDA's Center for Drug Evaluation and Research, outlined a number of tools to help biosimilar adoption. The resources provide basics such as the basic definition associated with biosimilars and what it means to be interchangeable, the standards of approval that biosimilars must go through, and easily accessible information on what the FDA is using to review biosimilarity.

Commissioner Gottlieb and Dr. Christl wrote, "an increase in market competition, offered by a growing complement of biosimilars, may lead to meaningfully reduced costs for both patients and our health care system."

The Centers for Medicare & Medicaid Services also plays a role in developing policy to spur biosimilar adoption. Dr. Mulcahy and his colleagues note work being done by the Medicare Payment Advisory Commission on recommendations that could address payment for physician-administered biosimilars under Part B, and incentives in the Part D program to steer patients and providers toward lower-cost biosimilars when appropriate. CMS changed current payment policy for biosimilars for 2018, which may have an effect.

"Beyond FDA regulation, payment, and coverage, both government and industry could play a role in educating patients and providers about the potential cost savings from biosimilars, much like both groups have done for generic drugs," they stated.

gtwachtman@frontlinemedcom.com

Treatment of fecal incontinence and defecatory disorders

BY AMY KARON
Frontline Medical News

About 25% of patients with fecal incontinence benefit from conservative treatments, which merit a "rigorous trial" before considering surgery, experts write in a Clinical Practice Update in the December issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.08.023).

"A stepwise approach should be followed for management of fecal incontinence. In our experience, many incontinent patients who are considered refractory to conservative therapy have not received an optimal trial of conservative therapy," states Adil E. Bharucha, MBBS, MD, of the Mayo Clinic and the Mayo Foundation in Rochester, Minn., and his associates.

Fecal incontinence affects 7%-15% of individuals and has potentially "devastating" implications for quality of life, the experts note. They recommend starting treatment by meticulously documenting bowel habits, triggers of incontinence, and treatment history. For fecal incontinence with diarrhea, they suggest eliminating caffeine and poorly absorbed dietary sugars, such as sorbitol and fructose, and adding loperamide, starting with one 2-mg tablet taken 30 minutes before breakfast and titrating up to a maximum of 16 mg per day.

Other conservative therapeutic options for diarrhea include fiber supplementation, scheduled toileting, a bowel retraining program, anticholinergic agents, clonidine, and cholestyramine or colesevelam to correct bile salt malabsorption.

Patients whose fecal incontinence involves constipation should start with laxatives and anorectal testing for evacuation disorders. Rectal cleansing with a small enema or tap water can help prevent stool leakage, the experts write.

If these conservative measures fail to improve fecal incontinence, they recommend anorectal manometry to test for anal weakness, reduced or increased rectal sensation, and impaired rectal balloon expulsion, all of which can improve with biofeedback therapy to retrain the pelvic floor. If biofeedback fails, consider perianal bulking agents, such as intra-anal injection of dextranomer, the experts suggest.

Sacral nerve stimulation might be indicated if moderate or severe fecal incontinence does not respond to at least 3 months of conservative treatment. However, the experts do not recommend percutaneous tibial nerve stimulation, which failed to outperform sham stimulation in a 12-week, double-blind, multicenter trial (Lancet. 2015;386:1640-8).

Surgery is indicated for fecal incontinence associated with major anatomic defects, such as rectovaginal fistula, full-thickness

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rectal prolapse, fistula in ano, or cloaca-like deformity. Additionally, sphincteroplasty is an option for postpartum women with fecal incontinence, patients with recent sphincter injuries, and patients with sphincter damage and fecal incontinence that fails to improve with conservative and biofeedback therapy, perianal bulking injection, and sacral nerve stimulation, according to the clinical practice update.

Barrier devices should be offered if fecal incontinence fails conservative treatments and surgery, or if surgery is not an option. Most anal plugs are "poorly tolerated," with two exceptions – a Food and Drug Administration–approved device from Renew Medical and a vaginal insert and pressure-regulated pump from Pelvalon. Colostomy might be indicated if patients with severe fecal incontinence fail conservative treatment and or are not candidates for barrier devices, minimally invasive surgeries, and sphincteroplasty.

If severe fecal incontinence is refractory to or contraindicated for all these interventions, the experts suggest considering artificial anal sphincter repair by dynamic graciloplasty.

If severe fecal incontinence is refractory to or contraindicated for all these interventions, the experts suggest considering artificial anal sphincter repair by dynamic graciloplasty. Surgery also is indicated to repair major anatomic defects such as rectovaginal fistula, full-thickness rectal prolapse, fistula in ano, or cloaca-like deformity, they noted.

A magnetic anal sphincter device is a possibility for patients with medically refractory severe fecal incontinence who have failed or are not candidates for barrier devices, perianal bulking injection, sacral nerve stimulation, sphincteroplasty, or a colostomy.

However, the study that led to FDA approval of a magnetic anal sphincter device included only 35 patients, and 7 (20%) had the device removed because of infection, erosion, or inefficacy. Another patient required a stoma in order to be able to defecate, and a total of 40% had moderate or severe complications when pain and bleeding were also considered, the experts noted.

Biofeedback is the preferred treatment for defecatory disorders – that is, chronic constipation or constipation-predominant irritable bowel syndrome with impaired rectal evacuation, according to the clinical practice update.

The experts recommend against sacral nerve stimulation, anterograde colonic enemas, and stapled transanal rectal resection for patients with defecatory disorders. Surgical treatment typically is reserved for the small minority of patients with considerable pelvic organ or rectal prolapse, they note.

The National Institutes of Health Sciences provided funding. The authors reported having no conflicts of interest.

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Huge database analysis affirms genes associated with NAFLD

BY DENISE FULTON
Frontline Medical News

WASHINGTON – A genome wide association study of the Million Veteran Program confirmed three specific genes associated with nonalcoholic fatty liver disease (NAFLD), underscoring the robustness of those loci.

Marina Serper, MD, of the Cpl. Michael J. Crescenz Veterans Affairs Medical Center, and University of Pennsylvania, both in Philadelphia, and her colleagues looked at patients with NAFLD in the Million Veterans Program (MVP), a project of the federal Precision Medicine Initiative designed to leverage the data associated with the Veterans Health Care Administration, Dr. Serper said at the annual meeting of the American Association for the Study of Liver Diseases.

About one-third (108,458) of 352,953 MVP enrollees whose DNA has been analyzed met the study definition of NAFLD. In their study, Dr. Serper and her associates defined the clinical phenotype of NAFLD as patients having abnormal alanine aminotransferase levels (greater than 30 U/L for men and greater than 20 U/L for women) detected twice in a 2-year period, plus at least one metabolic risk factor, such as body mass index of 30 kg/m^2 or greater, type 2 diabetes or prediabetes, hypertension, or dyslipidemia. Further, included patients did not have alcohol misuse disorders or viral hepatitis.

Frontline Medical News

Watch this video interview with Dr. Marina Serper for more information on the Million Veteran Program (gihepnews.com).

Most patients were male (90%) and white (72%), with a median age of 64 years. More than half (56%) had a BMI of 30 or greater, 30% were diagnosed with type 2 diabetes, and 71% with dyslipidemia, Dr. Serper said.

Logistic regression analysis adjusted for age, sex, and principal components stratified by ancestry (European, African American, and Hispanic). On initial analysis, 21 genetic loci met the criteria for genome wide significant association; specifically, investigators successfully replicated three key variants that were previously associated with NAFLD – PNPLA3, ERLIN1, and TRIB1.

"We were able to use clinical VA data to come up with a robust and clinically relevant definition and validate that definition because the genes we found associated with our definition of NAFLD have previously been shown by others who used biopsy data and imaging data for steatosis," Dr. Serper said in a video interview. "This is important because the diagnosis of fatty liver disease is really a clinical diagnosis."

The study was supported by the VA Office of Research and Development award 1I01BX003362. Dr. Serper had no conflicts.

dfulton@frontlinemedcom.com
On Twitter @denisefulton

Liver transplant center competition analyzed

BY ELI ZIMMERMAN
Frontline Medical News

WASHINGTON – Low market competition among liver transplant centers may affect which patients are considered too sick to transplant, according to a study presented at the annual meeting of the American Association for the Study of Liver Diseases.

With 20% of patients dying while on the transplant wait list, including those who were delisted, understanding the distribution of organs among donor service areas (DSAs) is crucial to lowering mortality during the current organ shortage, according to presenter Yanik Babekov, MD, of Massachusetts General Hospital, Boston.

Investigators studied 3,131 patients who were delisted after being classified as "too sick" from 116 centers in 51 DSAs, between 2002 and 2012.

Researchers used the Herfindahl-Hirschman Index (HHI), which analyzes the market share of each participant to determine the overall level of competition. Measurements on the HHI range between 0 and 1, with 0 being the most competitive and 1 being the least.

Frontline Medical News

In a video interview, Dr. Yanik Babekov discusses how competition among transplant centers affects delisting (gihepnews.com).

Mean delisting Model for End-Stage Liver Disease (MELD) scores considered to be "too sick to transplant" were 26.1, and average HHI among DSAs was 0.46, according to investigators. They found that, for every 1% increase in HHI, the delisting MELD score increased by 0.06, according to a risk-adjustment analysis.

"In other words, more competitive DSAs delist patients for [being] 'too sick' at lower MELD scores," Dr. Babekov explained in a video interview. While market competition may not be the only factor to explain the phenomenon of patients delisted for being "too sick," it is important to identify how having more transplant centers in DSAs can help more patients be added to, and stay on, these wait lists, according to investigators.

Dr. Babekov had no disclosures.

ezimmerman@frontlinemedcom.com
On Twitter @eaztweets

PRACTICE MANAGEMENT TOOLBOX: New opportunities for GI leadership in the evolving payment reform landscape

BY MARK JAPINGA, ROBERT S. SAUNDERS, PHD, ZIAD F. GELLAD, MD, MPH, AGAF, AND MARK MCCLELLAN, MD, PHD


MR. JAPINGA


DR. SAUNDERS


DR. GELLAD


DR. MCCLELLAN

This year's Congressional debate over repealing or reforming the Affordable Care Act was contentious in large part because of the high and rising costs of health care. Though a new health care reform bill is now unlikely, it remains critical to continue the discussion on how to deliver and pay for care in a way that addresses these costs and makes coverage more affordable through more efficient, high-quality approaches.[1]

On this front, there is bipartisan agreement on the direction of reform. Payment reform, through establishment of Alternative Payment Models (APMs), will continue to be the primary vehicle. APMs shift payments away from fee-for-service toward new models that better align incentives for physicians to provide more effective care while reducing waste, ensuring they remain accountable for patient results and total cost of care.[2] The new administration has reaffirmed its broad support of payment reform, an indication these programs will continue over the coming years.

The Medicare Access and CHIP Reauthorization Act (MACRA) passed with more than 90% support in both the House and Senate in 2015. MACRA provides a 5% bonus payment for physicians who receive a significant part of their Medicare payments in an advanced APM, which involves some downside financial risk. In addition, any physician who participates significantly in a broader range of Medicare APMs, including many without downside risk, receives an exception from the reporting requirements for the Merit-Based Incentive Payment System (MIPS) and would report on APM performance measures instead. However, the details of payment reform are challenging and will benefit from engagement and leadership by physicians – including in GI. A new survey shows that the Department of Health & Human Services has achieved its goal of having 30% of health care payments tied to APMs by the end of 2016.[3] It hopes to have 50% by the end of 2018.

The lack of available APMs for specialists, including GIs, is one of the greatest challenges going forward.[4] Some specialists can take part in an APM by participating in an Accountable Care Organization (ACO) – through the Medicare Shared Savings Program and related programs – or in a bundled episode payment model with downside risk. These options may be viable for some GIs employed by a hospital-based or integrated system, but they may not be practical or available for those in independent or smaller practices. Moreover, although a growing number of GIs participate in bundled episode payments for their commercial and Medicare Advantage patients, the Centers for Medicare & Medicaid Services (CMS) has not yet specified how this could count toward meeting APM requirements for MIPS exemptions or bonuses.

PTAC's role in recommending new payment models

The paucity of APMs was one reason MACRA law established the Physician-Focused Payment Model Technical Advisory Committee (PTAC). Organizations can submit proposals for new Medicare payment models to PTAC, which then are reviewed according to 10 established criteria. The criteria place particular emphasis on the scope of the APM, the APM's ability to increase quality while maintaining or decreasing costs, and whether the payment methodology improves on current policy. PTAC then makes recommendations to CMS for full implementation of a proposal, limited testing (a pilot program), or no implementation.

PTAC began accepting submissions in December 2016, reviewed its first proposals in April 2017, and reviewed three more in September. Two of the April proposals focused on GI care. Project Sonar, an intensive medical home designed to improve care coordination for patients with Crohn's disease, was recommended for limited testing. The Comprehensive Colonoscopy APM, which established episode-based payments for colonoscopies and cancer screening, was withdrawn before the meeting, after critical feedback from PTAC's preliminary reviews.

The fate of the two GI APMs offers broad insight on the path forward for new specialized-care models. Although PTAC focuses on physician payment, its criteria and critiques emphasize that the primary focus of any APM should be on the full spectrum of patient care. Project Sonar likely received a positive recommendation because it focused on shifting payment to improving chronic care and avoiding complications. Although the colonoscopy proposal was withdrawn, we can gain a sense of PTAC's concerns through the preliminary review.[5] The review argues the proposal did not sufficiently address how it would lead to a more efficient, better integrated, and higher-quality screening that improves patient health.

HHS does not have to follow PTAC's recommendation, and rejected it for Project Sonar largely because of the program's use of proprietary technology. PTAC has had similar debates over technology in other submissions, and this will be an important concern going forward. With no programs tested as of yet, PTAC and submitters will also benefit from more guidance on what limited testing looks like.

Implications for GI practice and planning

Further developments in several areas bear watching because they could accelerate opportunities for GIs. Most notable is the considerable payment model innovation underway in private health insurance and state Medicaid plans, models that could develop into PTAC submissions. Proj-

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ect Sonar was first implemented in collaboration with a private payer in Illinois. Similarly, the IBD specialty medical home was developed at the University of Pittsburgh. Both successfully have achieved the Triple Aim.[6] The private sector can serve as a testing ground for new APMs.

Second, working with both private and public payers, GIs could expand the concept of a specialty medical home or a primary-specialty coordinated medical home by incorporating more aspects of GI care. Chronic liver disease, chronic pancreatitis, and irritable bowel syndrome all could benefit from these approaches.[7] Medical home models generally include a shift from fee-for-service payments by providing per-patient payments (potentially risk-adjusted) to the coordinating physician for a period of time. That per-member per-month payment may enable additional patient-centric services such as extending access to care, regular patient outreach to monitor changes in health status, and partnering with primary care and other providers to help patients access treatment for comorbid conditions.

Third, as evidenced by the PTAC critique on the Comprehensive Colonoscopy APM, a revised approach is needed for bundled episode payment reforms to better support endoscopists focused on performing high-quality procedures. Given their procedural focus, these physicians will need to show the value of endoscopic services in well-coordinated patient care. These considerations generally suggest a broader episode payment model related to the goals of the procedure, rather than endoscopy-based bundles alone.

For example, a bundled payment for CRC screening, covering a full episode of treatment beyond a single colonoscopy, would make it easier for GIs to work more effectively with primary care providers to reduce gaps in CRC screening rates at the lowest cost. This bundle could be implemented by a specialized GI practice in conjunction with a primary care medical home or an ACO. If such a bundle is too much of a practice shift, an endoscopy-based episode payment could include performance measures and limited additional payments related to these same objectives.

GIs should look for further guidance from CMS on how bundled episode payments and other specialized-care payment reforms will interact with APMs for primary care, such as ACOs and the Project Sonar model recommended by PTAC.[8]

Despite the broader shift toward APMs, it remains likely that many GIs will participate in the fee-for-service–based MIPS program in the near term. Here, there may be opportunities to improve coordination in the MIPS program through additional care coordination payments for chronic disease, complementing the chronic care management payments that primary care physicians receive. Such payments would encourage further development and testing of outcome-oriented performance measures related to GI care.

Finally, GI care would benefit from better evidence for all GI-related payment reforms. Many of these reforms will be implemented outside of Medicare, but do not have results reported in a manner that makes it easy to assess their potential for broader implementation. Building an evidence base is feasible without imposing large costs or additional burdens on practices, especially when evaluations are implemented along with payment reforms, and offers the best way for organizations to learn and improve based on what works.[9]

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Take-away points

1. Despite the political divide over health care reform, there is bipartisan agreement on payment reform and controlling high health care costs through more efficient and high-quality approaches to delivering care.
2. CMS has encouraged the development of new payment models, especially to fill the gap in available models for specialty care. Organizations like the PTAC review new payment proposals and can recommend their implementation to CMS.
3. Early PTAC meetings show that the Committee wants to see models that emphasize care coordination and high-quality care and have a comprehensive focus; it is willing to approve programs with limitations to test them in the real world.
4. Gastroenterologists could take advantage of models like specialty medical homes or bundled payments to deliver more patient-centric care and better coordinate with primary care providers. Large and small practices alike could benefit from care coordination incentives that could help them improve outcomes.

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Conclusions

For accelerated progress toward health care payment reform, continued leadership from GIs is needed. Effective partnerships with primary care are particularly important to help avoid traditional gatekeeper approaches, and move toward a patient-centric model of shared accountability in which specialists function as a key partner in a medical neighborhood.[10] GIs can shape these steps, not only through PTAC and Medicare APMs, but through the other steps described earlier, and have a unique role in developing new models that leverage their specialty expertise.

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Mr. Japinga, Dr. Saunders, and Dr. McClellan are at the Duke-Margolis Center for Health Policy, Washington; Dr. Gellad is in the division of gastroenterology at the Duke University School of Medicine and at the Durham VA Medical Center, Durham, N.C. Dr. Gellad was supported by a Career Development Award from Veterans Affairs Health Services Research (CDA 14-158). The authors had no conflicts of interest.

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