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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

COURTESY DR. FASIHA KANWAL

Dr. Fasiha Kanwal and coauthors found that successful eradication of hepatitis C virus confers a benefit in DAA-treated patients.

Liver cancer risk lower after sustained response to DAAs

BY BIANCA NOGRADY
Frontline Medical News

Individuals with hepatitis C infection who achieved a sustained virologic response (SVR) to treatment with direct-acting antivirals had a significantly lower risk of hepatocellular carcinoma (HCC), a new study suggests.

A retrospective cohort study of 22,500 U.S. veterans with hepatitis C who had been treated with direct-acting antivirals (DAAs) found those with an SVR had a 72% lower risk of HCC, compared with those who did not achieve that response (hazard ratio, 0.28; 95% confidence interval, 0.22-0.36; *P* less than .0001), even after adjusting for demographics as well as clinical and health utilization factors.

The study showed the incidence of HCC among patients with SVR was 0.90/100 person-years, compared with 3.45/100 person-years in those without (Gastroenterology. 2017 Jun 19. doi: 10.1053/j.gastro.2017.06.012).

"These data show that successful eradication of HCV [hepatitis C virus] confers a benefit in DAA-treated

See **Liver Cancer** · *page 14*

AGA Clinical Practice Update: Opioids in GI

BY AMY KARON
Frontline Medical News

Physicians should consistently rule out opioid therapy as the cause of gastrointestinal symptoms, states a new clinical practice update published in the September 2017 issue of Clinical Gastroenterology and Hepatology (Clin Gastroenterol Hepatol. doi: 10.1016/j.cgh.2017.05.014).

About 4% of Americans receive long-term opioid therapy, primarily for musculoskeletal, postsurgical, or vascular pain, as well as nonsurgical abdominal pain, writes Michael Camilleri, MD, AGAF, of Mayo Clinic in Rochester, Minn., and his associates. Because opioid receptors thickly populate the gastrointestinal tract, exogenous opioids can trigger a variety of gastrointestinal symptoms. Examples include achalasia, gastroparesis, nausea, postsurgical ileus, constipation, and narcotic bowel syndrome.

Selective opioid use also can improve gastrointestinal symptoms in some disorders. Acute morphine use lowers resting lower esophageal sphincter (LES) pressure in both healthy and achalasic patients and inhibits transient LES relaxations in patients with gastroesophageal reflux disease, the experts note. However, chronic opioid therapy can impair LES relaxation and is also associated with

See **Opioids** · *page 4*

IBD rate higher among urban residents

BY ELI ZIMMERMAN
Frontline Medical News

Children born in urban areas are more likely to develop inflammatory bowel disease (IBD) when they grow up than are children born in rural areas, a Canadian study showed.

With rising rates of IBD in developing nations and urbanized areas, the investigators interpreted these findings as a positive step toward further understanding, and eventually eliminating, the risk of developing IBD.

"Exposure to the rural environment from birth was consistently associated with a strong protective association with the development of IBD later in life, whether children were exposed continuously for 1-5 years from birth," according to Eric I. Benchimol, MD, PhD, a

See **Urban** · *page 15*

News from DDW2017 Digestive Disease Week® in this issue

INSIDE

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DDSEPeight Quick quiz

Digestive Diseases Self-Education Program

Q1: A 56-year-old woman with a history of scleroderma presents for evaluation of recurrent episodes of bloating, excess flatulence, mild nausea, and watery diarrhea for the past 5 months without associated weight loss, gastrointestinal bleeding, or fevers.

She had a normal screening colonoscopy 2 years ago, and an upper endoscopy for evaluation of reflux and dyspepsia 5 years ago, which was only notable for a small sliding hiatal hernia. Laboratory testing reveals hemoglobin of 10.9 g/dL with an MCV 106 fL. Stool studies are negative for occult blood, fecal calprotectin is not elevated, but a Sudan stain is positive.

Which of the following is the best next step?

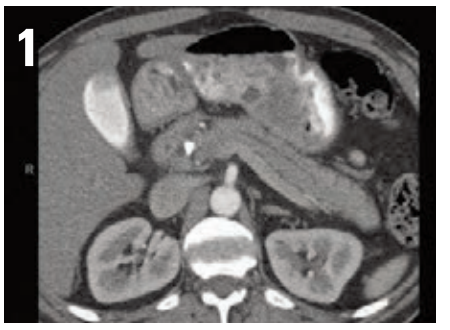
A. *Helicobacter pylori* stool antigen testing
B. Tissue transglutaminase antibody testing
C. Colonoscopy with random biopsies
D. Hydrogen breath testing
E. Magnetic resonance enterography

Q2: A 72-year-old man is admitted to the hospital with mild acute pancreatitis. He reports vague abdominal pain for the past 3 months. He is otherwise healthy and has well-controlled hypertension. He is active and exercises three times a week. CT scan reveals a markedly dilated main pancreatic duct with no stricture as shown below in representative axial and coronal images (Figures 1, 2).

What is the next best step in the management of this patient?

A. EUS with fine-needle aspiration
B. Surgical consultation for total pancreatectomy
C. ERCP with pancreatic duct brushings
D. Clinical observation with further imaging based on symptoms
E. Surveillance with MRI in 3 months

The answers are on page 16.



AGA Institute

LETTER FROM THE EDITOR: Maintain a sense of hope

For many of us, September brings a sense of closure (summer) and anticipation (return of students, fall). The solace August usually brings has, this year, been interrupted by national events, including continuing legislative assaults on the Affordable Care Act, threats of another war, and the events in Charlottesville, Va., among others. Throughout all of this, *GI & Hepatology News* and the AGA will try and provide you real news, science-based thinking, and unbiased reporting so that you can provide best care to the people that come to you for digestive help.

One of our lead articles concerns opioid medications. Evidence is beginning to point to fundamental drivers of opioid addiction and one of them appears to be us (physicians). According to a review of federal records, 1 in 12 physicians received monetary payments from companies that produce opioids. We were taught that pain was the fifth vital sign, relieving pain was a priority, and new opiate formulations could be used safely for chronic, nonmalignant pain. We are now seeing the unintended consequences of these concepts. The AGA has provided a new Clinical Practice Update about opioids in gastroenterology (http://dx.doi.org/10.1016/j.cgh.2017.05.014) published in *Clinical Gastroenterology and Hepatology.*

Elsewhere in the issue, we present important information about hepatocellular carcinoma, inflammatory bowel disease (risk factors, drug monitoring, IBD therapies), Barrett's esophagus, and summaries from the 2017 AGA Postgraduate Course.

DR. ALLEN

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

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FRONTLINE MEDICAL COMMUNICATIONS

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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.

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Digestive side effects the norm

Opioids *from page 1*

high amplitude/velocity and simultaneous esophageal waves, outflow obstruction at the esophagogastric junction, higher integrated relaxation pressure, and lower distal latency on esophageal pressure topography.

In the stomach, opioid use can cause gastroparesis, early satiety, and postprandial nausea and emesis, especially in the postoperative setting. Even novel opioid agents that are less likely to cause constipation can retard gastric emptying. For example, tapentadol, a mu-opioid agonist and norepinephrine reuptake inhibitor, delays emptying to the same extent as oxycodone. Tramadol also appears to slow overall orocecal transit. Although gastroparesis itself can cause nausea and emesis, opioids also directly stimulate the chemoreceptor trigger zone in the area postrema in the floor of the fourth ventricle. Options for preventive therapy include using a prokinetic, such as metoclopramide, prochlorperazine, or a 5-hydroxytryptamine$_3$ antagonist, especially if patients are receiving opioids for postoperative pain control.

Exogenous opioids also can cause ileus, especially after abdominal surgery. These patients are already

Dr. Michael Camilleri

at risk of ileus because of surgical stress from bowel handling, secretion of inflammatory mediators and endogenous opioids, and fluctuating hormone and electrolyte levels. Postoperative analgesia with mu-opioids adds to the risk of ileus by increasing fluid absorption and inhibiting colonic motility.

Both postsurgical and nonsurgical opioid use also can trigger opioid-induced constipation (OIC), in which patients have less than three spontaneous bowel movements a week, harder stools, increased straining, and a feeling of incomplete evacuation. Patients may also report nausea, emesis, and gastroesophageal reflux. Even low-dose and short-term opioid therapy can lead to OIC.

Symptoms and treatment response can be assessed with the bowel function index, in which patients rate ease of defecation, completeness of bowel evacuation, and severity of constipation over the past week on a scale of 0-100. Scores of 0-29 suggest no OIC. Patients who score above 30 despite over-the-counter laxatives are candidates for stepped-up treatments, including prolonged-release naloxone and oxycodone, the intestinal secretagogue lubiprostone, or peripherally acting mu-opioid receptor antagonists (PAMORAs), such as methylnaltrexone (12 mg subcutaneously) and naloxegol (12.5 mg or 25 mg per day orally). Additionally, tapentadol controls pain at lower doses than oxycodone and is less

likely to cause constipation.

Narcotic bowel syndrome typically presents as moderate to severe daily abdominal pain lasting more than 3 months in patients on long-term opioids equating to a dosage of more than 100 mg morphine daily. Typically, patients report generalized, persistent, colicky abdominal pain that does not respond to dose escalation and worsens with dose tapering. Work-up is negative for differentials such as kidney stones or bowel obstruction. One epidemiological study estimated that 4% of patients on long-term opiates develop narcotic bowel syndrome, but the true prevalence may be higher, according to the experts who authored this update. Mechanisms remain unclear but may include neuroplastic changes that favor the facilitation of pain signals rather than their inhibition, inflammation of spinal glial cells through activation of toll-like receptors, abnormal function of the N-methyl-D aspartate receptor at the level of the spinal cord, and central nociceptive abnormalities related to certain psychological traits or a history of trauma.

Narcotic bowel syndrome typically presents as moderate to severe daily abdominal pain lasting more than 3 months in patients on long-term opioids equating to a dosage of more than 100 mg morphine daily.

Treating narcotic bowel syndrome requires detoxification with appropriate nonopioid therapies for pain, anxiety, and withdrawal symptoms, including the use of clonidine. "This is best handled through specialists or centers with expertise in opiate dependence," the experts stated. Patients who are able to stay off narcotics report improvements in pain, but the recidivism rate is about 50%.

The practice update also covers opioid therapy for gastrointestinal disorders. The PAMORA alvimopan shortens time to first postoperative stool without counteracting opioid analgesia during recovery. Alvimopan also has been found to hasten recovery of gastrointestinal function in patients with postoperative ileus after bowel resection. There is no evidence for using mu-opioid agonists for pain associated with irritable bowel syndrome (IBS), but the synthetic peripheral mu-opioid receptor agonist loperamide can improve stool consistency and urgency. A typical dose is 2 mg after each loose bowel movement or 2-4 mg before eating in cases of postprandial diarrhea. The mixed mu- and kappa-opioid receptor agonist and delta-opioid receptor antagonist eluxadoline also can potentially improve stool consistency and urgency, global IBS symptoms, IBS symptom severity score, and quality of life. However, the FDA warns against using eluxadoline in patients who do not have a gallbladder because of the risk of severe outcomes – including death – related to sphincter of Oddi spasm and pancreatitis. Eluxadoline has been linked to at least two such fatalities in cholecystectomized patients. In each case, symptoms began after a single dose.

Dr. Camilleri is funded by the National Institutes of Health. He disclosed ties to AstraZeneca and Shionogi. The two coauthors disclosed ties to Forest Research Labs, Ironwood Pharmaceuticals, Prometheus, and Salix.

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FLASHBACK TO 2015

2007-**10-Year Anniversary**-2017

In the early 1970s, clindamycin had only been on the market for a few years when patients taking the antibiotic began to present with diarrhea and associated colitis. Initial attempts to culture a pathologic organism were unsuccessful, so other possible pathophysiologic mechanisms, including medication toxicity, altered bacterial flora, or the emergence of a new bacterial or viral pathogen were considered. Patients were initially given treatments similar to those for ulcerative colitis, with systemic and topical steroids and colectomy. Several years later, *Clostridium difficile* infection (CDI) was identified as the culprit, and these presentations became increasingly common in U.S. hospitals, and later in community settings.

Incidentally, the organism had been discovered years earlier, in 1935, by a group of scientists studying normal bacterial flora in neonates, but it was not known to be pathogenic in adults. By 2007, CDI had become the most common cause of health care–associated infection in U.S. hospitals. This prompted the Centers for Disease Control and Prevention to begin active population- and laboratory-based surveillance for *C. difficile* through its Emerging Infections Program (EIP) with the goal of more accurately assessing disease burden, incidence, recurrence, and mortality by capturing data across the spectrum of health care delivery settings. The April 2015 issue of *GI & Hepatology News* highlighted a report of 2011 CDC data from 10 EIP sites (N Engl J Med. 372;9:825-34), demonstrating that CDI was responsible for nearly half a million infections and 29,000 deaths in that year across sites, with the hypervirulent NAP1 strain found to be more prevalent among health care–associated than community-associated infections.

Treatment of CDI continues to evolve. With increased use of fecal microbiota transplantation, emerging evidence regarding the efficacy of other novel therapies such as the monoclonal antibodies actoxumab and bezlotoxumab (providing passive immunity to toxins A and B, respectively), and development of preventive vaccines (currently in phase 2 trials), there is hope on the horizon of being able to improve patient outcomes and reduce the burden of CDI on the health care system.

Megan A. Adams, MD, JD, MSc, is a clinical lecturer in the division of gastroenterology at the University of Michigan, a gastroenterologist at the Ann Arbor, Mich., VA, and an investigator in the VA Ann Arbor Center for Clinical Management Research. She is an associate editor of GI & Hepatology News.

FROM THE AGA JOURNALS

Large distal nongranular colorectal polyps were most likely to contain occult invasive cancers

BY AMY KARON
Frontline Medical News

Large sessile or flat colorectal polyps or laterally spreading lesions were most likely to contain covert malignancies when their location was rectosigmoid, their Paris classification was 0-Is or 0-IIa+Is, and they were nongranular, according to the results of a multicenter prospective cohort study of 2,106 consecutive patients reported in the September issue of Gastroenterology (doi: 10.1053/j.gastro.2017.05.047).

"Distal nongranular lesions have a high risk of occult SMIC [submucosal invasive cancer], whereas

Continued on following page

In recent years, substantial efforts have been made to improve both colonoscopy preparation and endoscopic image quality to achieve improved polyp detection. In addition, while large, complex colon polyps (typically greater than 20 mm in size) previously were often referred for surgical resection, improved polyp resection techniques and equipment have led to the ability to remove many such lesions via endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).

However, while much attention has deservedly been focused on improving our ability to detect and resect colon polyps, efforts focusing on optimizing the inspection and characterization of large colorectal polyps or laterally spreading lesions to determine resectability have received less attention. This intermediate step between detection and resection is critical, as it can determine whether endoscopic resection is likely to be curative or if surgery will be necessary. Overt visual features that suggest invasive (into the submucosa or deeper) cancer that would warrant surgery include the Kudo V pit pattern and the presence of depressed or excavated lesions (Paris classification 0-IIc and III). However, little information regarding predictors of submucosal invasive cancer exists for patients without endoscopic criteria for invasion. In this study of 2,277 nonserrated lesions in 2,106 patients, Dr. Burgess and colleagues aimed to answer this question and identified four key features associated with "covert" submucosal invasive cancer in these polyps. They include a rectosigmoid location, Paris classification, surface morphology (granular vs. nongranular), and increasing size.


DR. MUTHUSAMY

The authors are to be congratulated for their meticulous and sustained efforts in acquiring and analyzing this data. These results provide endoscopists with some important, practical, and entirely visual criteria to assess upon identification of large colon polyps that can aid in determining which type of endoscopy therapy, if any, to embark upon. Avoiding EMR when there is a reasonably high probability of invasive disease will allow for choosing a more appropriate technique such as ESD (which is becoming increasingly available in the West) or surgery. In addition, patients can avoid the unnecessary EMR-related risks of bleeding and perforation when this technique is likely to result in an inadequate resection. Future work should assess whether this information can be widely adopted and utilized to achieve similar predictive accuracy in nonexpert settings.

V. Raman Muthusamy, MD, MAS, AGAF, is director of endoscopy, professor of clinical medicine, University of California, David Geffen School of Medicine at UCLA. He is a consultant for Medtronic and Boston Scientific.

FROM THE AGA JOURNALS

Continued from previous page

proximal, granular 0-IIa lesions, after a careful assessment for features associated with SMIC, have a very low risk," wrote Nicholas G. Burgess, MD, of Westmead Hospital, Sydney, with his associates. "These findings can be used to inform decisions [about] which patients should undergo endoscopic submucosal dissection, endoscopic mucosal resection, or surgery."

Many studies of colonic lesions have examined predictors of SMIC. Nonetheless, clinicians need more information on factors that improve clinical decision making, especially as colonic endoscopic submucosal dissection becomes more accessible, the researchers said. Large colonic lesions can contain submucosal invasive SMICs that are not visible on endoscopy, and characterizing predictors of this occurrence could help patients and clinicians decide between endoscopic submucosal dissection and endoscopic mucosal resection. To do so, the researchers analyzed histologic specimens from 2,277 colonic lesions above 20 mm (average size, 37 mm) that lacked overt endoscopic high-risk features. The study ran from 2008 through 2016, study participants averaged 68 years of age, and 53% were male.

A total of 171 lesions (8%) had evidence of SMIC on pathologic review, and 138 lesions had covert SMIC. Predictors of overt and occult SMIC included Kudo pit pattern V, a depressed component (0-IIc), rectosigmoid location, 0-Is or 0-IIa+Is Paris classification, nongranular surface morphology, and larger size. After excluding lesions with obvious SMIC features – including serrated lesions and those with depressed components (Kudo pit pattern V and Paris 0-IIc) – the strongest predictors of occult SMIC included Paris classification, surface morphology, size, and location.

"Proximal 0-IIa G or 0-Is granular lesions had the lowest risk of SMIC (0.7% and 2.3%), whereas distal 0-Is nongranular lesions had the highest risk (21.4%)," the investigators added. Lesion location, size, and combined Paris classification and surface topography showed the best fit in a multivariable model. Notably, rectosigmoid lesions had nearly twice the odds of containing covert SMIC, compared with proximal lesions (odds ratio, 1.9; 95% confidence interval, 1.2-3.0; $P = .01$). Other significant predictors of covert SMIC in the multivariable model included combined Paris classification, surface morphology (OR, 4.0; 95% CI, 1.2-12.7; $P = .02$), and increasing size (OR, 1.2 per 10-mm increase; 95% CI, 1.04-1.3; $P = .01$). Increased size showed an even greater effect in lesions exceeding 50 mm.

Clinicians can use these factors to help evaluate risk of invasive cancer in lesions without overt SMIC, the researchers said. "One lesion type that differs from the pattern is 0-IIa nongranular lesions," they noted. "Once lesions with overt evidence of SMIC are excluded, these lesions have a low risk (4.2%) of harboring underlying cancer." Although 42% of lesions with covert SMIC were SM1 (potentially curable by endoscopic resection), no predictor of covert SMIC also predicted SMI status.

'Proximal 0-IIa G or 0-Is granular lesions had the lowest risk of SMIC (0.7% and 2.3%), whereas distal 0-Is nongranular lesions had the highest risk (21.4%).'

Funders included Cancer Institute of New South Wales and Gallipoli Medical Research Foundation. The investigators had no conflicts of interest.

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Minimally invasive screening for Barrett's esophagus offers cost-effective alternative

BY AMY KARON
Frontline Medical News

The high costs of endoscopy make screening patients with gastroesophageal reflux disease (GERD) for Barrett's esophagus a costly endeavor. But using a minimally invasive test followed by endoscopy only if results are positive could cut costs by up to 41%, according to investigators.

The report is in the September issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.02.017).

The findings mirror those from a prior study (Gastroenterology. 2013 Jan;144[1]:62-73.e60) of the new cytosponge device, which tests surface esophageal tissue for trefoil factor 3, a biomarker for Barrett's esophagus, said Curtis R. Heberle, of Massachusetts General Hospital in Boston, and his associates. In addition, two separate models found the cytosponge strategy cost effective compared with no screening (incremental cost-effectiveness ratios [ICERs], about $26,000-$33,000). However, using the cytosponge instead of screening all GERD patients with endoscopy would reduce quality-adjusted life-years (QALYs) by about 1.8-5.5 years for every 1,000 patients.

Rates of esophageal adenocarcinoma have climbed more than sixfold in the United States in 4 decades, and 5-year survival rates remain below 20%. Nonetheless, the high cost of endoscopy and 10%-20% prevalence of GERD makes screening all patients for Barrett's esophagus infeasible. To evaluate the cytosponge strategy, the researchers fit data from the multicenter BEST2 study (PLoS Med. 2015 Jan; 12[1]: e1001780) into two validated models calibrated to high-quality Surveillance, Epidemiology and End Results (SEER) data on esophageal cancer. Both models compared no screening with a one-time screen by either endoscopy alone or cytosponge with follow-up endoscopy in the event of a positive test. The models assumed patients were male, were 60 years old, and had GERD but not esophageal adenocarcinoma.

Without screening, there were about 14-16 cancer cases and about 15,077 quality-adjusted life years (QALYs) for every 1,000 patients. The cytosponge strategy was associated with about 8-13 cancer cases and about 15,105 QALYs. Endoscopic screening produced the most benefit overall – only about 7-12 cancer cases, with more than 15,100 QALYs. "However, greater benefits were accompanied by higher total costs," the researchers said. For every 1,000 patients, no screening cost about $704,000 to $762,000, the cytosponge strategy cost about $1.5 million to $1.6 million, and population-wide endoscopy cost about $2.1 million to $2.2 million. Thus, the cytosponge method would lower the cost of screening by 37%-41% compared with endoscopically screening all men with GERD. The cytosponge was also cost effective in a model of 60-year-old women with GERD.

Using only endoscopic screening was not cost effective in either model, exceeding a $100,000 threshold of willingness to pay by anywhere from $107,000 to $330,000. The cytosponge is not yet available commercially, but the investigators assumed it cost $182 based on information from the manufacturer (Medtronic) and Medicare payments for similar devices. Although the findings withstood variations in indirect costs and age at initial screening, they were "somewhat sensitive" to variations in costs of the cytosponge and its presumed sensitivity and specificity in clinical settings. However, endoscopic screening only became cost effective when the cytosponge test cost at least $225.

The models assumed perfect adherence to screening, which aprobably exaggerated the effectiveness of the cytosponge and endoscopic screening, the investigators said. They noted that cytosponge screening can be performed without sedation during a short outpatient visit.

The National Institutes of Health provided funding. The investigators had no relevant disclosures.

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FROM THE AGA JOURNALS

Study highlights risks of postponing cholecystectomy

BY AMY KARON
Frontline Medical News

Almost half of patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) did not undergo cholecystectomy (CCY) within the next 60 days, according to the results of a large, retrospective cohort study reported in the September issue of Gastroenterology (doi: 10.1053/j.gastro.2017.05.048).

"Although early and delayed CCY equally reduce the risk of subsequent recurrent biliary events, patients are at 10-fold higher risk of a recurrent biliary event while waiting for a delayed CCY, compared with patients who underwent early CCY," wrote Robert J. Huang, MD, and his associates of Stanford (Calif.) University Medical Center. Delayed CCY is cost effective, but that benefit must be weighed against the risk of loss to follow-up, especially if patients have "little or no health insurance," they said.

Gallstone disease affects up to 15% of adults in developed societies, including about 20-25 million Americans. Yearly costs of treatment tally at more than $6.2 billion and have risen by more than 20% in 3 decades, according to multiple studies. Approximately 20% of patients with gallstone disease have choledocholithiasis, mainly because gallstones can pass from the gallbladder into the common bile duct. After undergoing ERCP, such patients are typically referred for CCY, but there are no "societal guidelines" on timing the referral, the researchers said. Practice patterns remain "largely institution based and may be subject to the vagaries of surgeon availability and other institutional resource constraints." One prior study linked a median 7-week wait time for CCY with a 20% rate of recurrent biliary events. To evaluate large-scale practice patterns, the researchers studied 4,516 patients who had undergone ERCP for choledocholithiasis in California (during 2009-2011), New York (during 2011-2013), and Florida (during 2012-2014) and calculated timing and rates of subsequent CCY, recurrent biliary events, and deaths. Patients were followed for up to 365 days after ERCP.

Of the 4,516 patients studied, 1,859 (41.2%) patients underwent CCY during their index hospital admission (early CCY). Of the 2,657 (58.8%) patients who were discharged without CCY, only 491 (18%) had a planned CCY within 60 days (delayed CCY), 350 (71.3%) of which were done in an outpatient setting. Of the patients in the study, 2,168 (48.0%) did not have a CCY (no CCY) during their index visit or within 60 days. Over 365 days of follow-up, 10% of patients who did not have a CCY had recurrent biliary events, compared with 1.3% of patients who underwent early or delayed CCY. The risk of recurrent biliary events for patients who underwent early or delayed CCY was about 88% lower than if they had had no CCY within 60 days of ERCP (*P* less than .001 for each comparison). Performing CCY during index admission cut the risk of recurrent biliary events occurring within 60 days by 92%, compared with delayed or no CCY (*P* less than .001).

In all, 15 (0.7%) patients who did not undergo CCY died after subsequent hospitalization for a recurrent biliary event, compared with 1 patient who underwent early CCY (0.1%; *P* less than .001). There were no deaths associated with recurrent biliary events in the delayed-CCY group. Rates of all-cause mortality over 365 days were 3.1% in the no-CCY group, 0.6% in the early-CCY group, and 0% in the delayed-CCY group. Thus, cumulative death rates were about seven times higher among patients who did not undergo CCY compared with those who did (*P* less than .001).

Patients who did not undergo CCY tended to be older than delayed- and early-CCY patients (mean ages 66 years, 58 years, and 52 years, respectively). No-CCY patients also tended to have more comorbidities. Nonetheless, having an early CCY retained a "robust" protective effect against recurrent biliary events after accounting for age, sex, comorbidities, stent placement, facility volume, and state of residence. Even after researchers adjusted for those factors, the protective effect of early CCY dropped by less than 5% (from 92% to about 87%), the investigators said.

They also noted that the overall cohort averaged 60 years of age and that 64% were female, which is consistent with the epidemiology of biliary stone disease. Just over half were non-Hispanic whites. Medicare was the single largest primary payer (46%), followed by private insurance (28%) and Medicaid (16%).

"A strategy of delayed CCY performed on an outpatient basis was least costly," the researchers said. "Performance of early CCY was inversely associated with low facility volume. Hispanic race, Asian race, Medicaid insurance, and no insurance associated inversely with performance of delayed CCY."

Funders included a seed grant from the Stanford division of gastroenterology and hepatology and the National Institutes of Health. The investigators had no conflicts of interest.

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High myristic acid intake tied to relapse in ulcerative colitis

BY AMY KARON
Frontline Medical News

High intake of myristic acid approximately tripled the odds of relapse in patients with ulcerative colitis (UC), compared with low intake, according to the results of a 12-month multicenter, prospective, observational study reported in the September 2017 issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.12.036).

Relapsers consumed an average of 2.2 g of this saturated fatty acid daily from sources such as palm and coconut oils, as well as dairy fats, reported Edward L. Barnes, MD, MPH, and his associates at Brigham and Women's Hospital, Boston, on behalf of the DREAM (Diet's Role in Exacerbations of Mesalamine Maintenance) investigators. Nonrelapsers averaged 1.4 g/day.

Dietary factors are thought to underlie relapse in UC, but specific culprits are poorly defined, the investigators said. Therefore, the DREAM study prospectively tracked dietary intake and flares among a homogeneous group of 412 patients with UC from 25 academic and community gastroenterology practices in the United States. Between 2007 and 2014, patients were interviewed by telephone every 3 months for 1 year or until they reported a flare, defined as a Simple Clinical Colitis Activity Index score of at least 5 or a change in disease activity that entailed a change in medication.

A total of 34 patients were lost to follow-up, and 45 (11% of those remaining) flared within a year of study enrollment. "When analyzed in tertiles, increasing intake of multiple fatty acids was associated with increasing odds of relapse," the researchers wrote. Predictors of flare in the univariate analysis included high intake of myristic acid, oleic acid, eicosenoic acid, palmitelaidic acid, total translinoleic acid, saturated fat, monounsaturated fat, and omega-3 fatty acids. Only high intake of myristic acid maintained a significant dose-response relationship in the multivariable analysis (odds ratio, 3.0; 95% confidence interval, 1.2-7.7; *P* = .02 for high vs. low intake). Moderate intake of alpha-linolenic acid predicted flare (OR, 5.5; 95% CI, 1.6-19.3; *P* = .001) in the multivariable analysis, but high intake did not (OR, 1.3; 95% CI, 0.3-7.0; *P* = .4). "Other foods previously implicated in flares of UC, such as processed meat, alcohol, and foods high in sulfur, were not associated with an increased risk of flare," the researchers wrote.

Study participants were generally in their mid- to late 40s, white, and not current smokers. More than half were male. Most had proctitis or left-sided colitis, not pancolitis. Relapsers averaged 2.4 flares in the

Continued on following page

FROM THE AGA JOURNALS

Continued from previous page

18 months before enrollment (standard deviation, 1.9), compared with 1.8 flares for nonrelapsers (SD, 2.4; $P = .003$).

This study was subject to unmeasured confounding and also excluded many types of patients: anyone with a history of allergy to salicylates, aminosalicylates, or mesalamine tablets. Also excluded were those who had recent exposure to NSAIDs, antibiotics, antidiarrheals, antispasmodics, immunosuppressives, biologics, or corticosteroids (except budesonide). Requiring monotherapy with an aminosalicylate might limit the generalizability of the findings, the investigators noted. Patients were on variable doses of aminosalicylates, and higher doses might have helped inhibit flares.

Actavis and the National Institutes of Health provided funding. The investigators reported having no relevant financial conflicts.

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Patients with IBD commonly ask their physicians if dietary modifications can be made to control their disease. Despite the interest from patients, we have limited data to provide informed recommendations.

DR. SHAH

Barnes and colleagues reported results from a prospective, multicenter, observational study of more than 400 adult patients with UC in remission with aminosalicylates.

They obtained food-frequency questionnaires and were able to associate macro- and micronutrients with the risk of subsequent flares. Eleven percent of patients experienced a flare during the 1-year observation period. In their multivariate analysis, patients with a high intake of foods with myristic acid had a threefold higher risk of flare, compared with the lowest intake group. These findings suggest avoidance of foods such as palm oil, coconut oil, and some dairy products may reduce the risk of flares. These results emphasize the potential for dietary components to modify the risk of flare but also the difficulty of integrating and interpreting these findings with prior studies.

These results provide new information to better guide our discussions with patients regarding diet and disease activity. However, the body of information remains sparse, and we should reinforce that dietary manipulation is an adjunct measure, at best, to our current medical therapies.

Rajesh Rasik Shah, MD, is assistant professor of medicine, gastroenterology and hepatology at Baylor College of Medicine, Houston; staff physician at Michael E. Debakey VA Medical Center. He has no conflicts of interest.

FROM THE AGA JOURNALS

Colonic microbiota encroachment linked to diabetes

BY AMY KARON
Frontline Medical News

BACTERIAL INFILTRATION into the colonic mucosa was associated with type 2 diabetes mellitus in humans, confirming prior findings in mice, investigators said.

Unlike in mice, however, microbiota encroachment did not correlate with human adiposity per se, reported Benoit Chassaing, PhD, of


DR. FREY

Dr. Chassaing and his colleagues examined the possible importance of the bacteria-free layer adjacent to the colonic epithelium in metabolic syndrome. A shrinking of this layer, termed "bacterial encroachment," has been associated with human IBD as well as mouse models of colitis and metabolic syndrome, but the current study represents its first clear demonstration in human diabetes. In a cohort of 42 patients, the authors found that the epithelial-bacterial distance was inversely correlated with BMI, fasting glucose, and hemoglobin A_{1c} levels.

The primary predictor of encroachment in these patients was dysglycemia, not BMI. This could not have been tested in standard mouse models where, because of the nature of the experimental insult, obesity and dysglycemia are essentially linked. Comparing obese human patients with and without dysglycemia, however, showed that encroachment is only clearly correlated with failed glucose regulation. But in coordinated experiments with a short-term murine dysglycemia model, high glucose levels were not sufficient to elicit encroachment, suggesting a more complex metabolic circuit as the driver.

Going forward, a key question will be whether the narrowed sterile layer above the epithelium is a cause or consequence of low-grade intestinal inflammation and chronic metabolic changes. Bacterial encroachment also may be part of the mechanism for the inflammatory effects of dietary emulsifiers, which the authors previously showed can drive colitis.

Mark R. Frey, PhD, is associate professor of pediatrics, biochemistry, and molecular medicine at the Saban Research Institute, Children's Hospital Los Angeles, USC. He has no conflicts of interest.

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FROM THE AGA JOURNALS

Georgia State University, Atlanta, and his associates. Their mouse models all have involved low-grade inflammation, which might impair insulin/leptin signaling and thereby promote both adiposity and dysglycemia, they said. In contrast, "we presume that humans can become obese for other reasons not involving the microbiota," they added. The findings were published in the September issue of Cellular and Molecular Gastroenterology and Hepatology (2017;2[4]:205-21. doi: 10.1016/j.jcmgh.2017.04.001).

For the study, the investigators analyzed colonic mucosal biopsies from 42 middle-aged diabetic adults who underwent screening colonoscopies at a single Veterans Affairs hospital. All but one of the patients were men, 86% were overweight, 45% were obese, and 33% (14 patients) had diabetes. The researchers measured the shortest distance between bacteria and the epithelium using confocal microscopy and fluorescent in situ hybridization.

Nonobese, nondiabetic patients had residual bacteria "almost exclusively" in outer regions of the mucus layer, while obese diabetic patients had bacteria in the dense inner mucus near the epithelium, said the investigators. Unlike in mice, bacterial-epithelial distances did not correlate with adiposity per se among individuals without diabetes ($P = .4$). Conversely, patients with diabetes had bacterial-epithelial distances that were about one-third of those in euglycemic individuals (P less than .0001), even when they were not obese (P less than .001).

"We conclude that microbiota encroachment is a feature of insulin resistance–associated dysglycemia in humans," Dr. Chassaing and his associates wrote. Microbiota encroachment did not correlate with ethnicity, use of antibiotics or diabetes treatments, or low-density lipoprotein levels, but it did correlate with a rise in CD19+ cells, probably mucosal B cells, they said. Defining connections among microbiota encroachment, B-cell responses, and metabolic disease might clarify the pathophysiology and treatment of metabolic syndrome, they concluded.

The investigators also induced hyperglycemia in wild-type mice by giving them water with 10% sucrose and intraperitoneal streptozotocin injections. Ten days after the last injection, they measured fasting blood glucose, fecal glucose, and colonic bacterial-epithelial distances. Even though fecal glucose rose as expected, they found no evidence of microbiota encroachment. They concluded that short-term (2-week) hyperglycemia was not enough to cause encroachment. Thus, microbiota encroachment is a characteristic of type 2 diabetes, not of adiposity per se, correlates with disease severity, and might stem from chronic inflammatory processes that drive insulin resistance, they concluded.

Funders included the National Institutes of Health, VA-MERIT, and the Crohn's and Colitis Foundation of America. The investigators had no relevant conflicts of interest.

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What are the complications of PPI therapy?

Talking to your patients about PPIs
AGA has developed talking points about research released associating PPIs with dementia, chronic kidney disease, and the latest research associating PPI use with all-cause mortality. These resources can help you educate your patients on the data and on the risks and benefits of using PPIs in their care.

- PPIs and dementia: http://www.gastro.org/news_items/2017/07/20/how-to-talk-with-your-patients-about-ppis-and-dementia.
- PPIs and chronic kidney disease: http://www.gastro.org/news_items/how-to-talk-with-patients-about-ppis-and-chronic-kidney-disease.
- PPIs and all-cause mortality: http://www.gastro.org/news_items/a-guide-to-conversations-about-the-latest-ppi-research-results.

Talking to your colleagues about PPIs
AGA members have been discussing this new data linking PPIs to death. Weigh in by visiting the AGA Community, www.community.gastro.org.

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25 years of groundbreaking gastric cancer research

In 1992, the AGA Research Foundation issued the first AGA-R. Robert and Sally D. Funderburg Research Award in Gastric Cancer to support research into this previously underfunded area. There have been 26 recipients of the AGA-Funderburg award to date, comprising an honor roll of distinguished national leaders in gastroenterology. Each recipient has addressed different aspects of the disease, providing a dramatic improvement in the understanding and treatment of gastric cancer.

The AGA Research Foundation is thankful for the continuous funding from the Funderburg family, which has provided the opportunity for gastric cancer research discoveries that otherwise would not have been funded. Learn more about the Funderburgs and the impact of this award in AGA Perspectives, http://agaperspectives.gastro.org/reflecting-25-years-groundbreaking-gastric-cancer-research.

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AGA–R. Robert and Sally D. Funderburg Research Award in Gastric Cancer Recipients

Year	AGA-Funderburg Recipient	Year	AGA-Funderburg Recipient
1992	C. Richard Boland, MD, AGAF	2005	JeanMarie Houghton, MD, PhD
1993	Brian J. Reid, MD, PhD	2006	Steven H. Itzkowitz, MD, AGAF
1994	Timothy C. Wang, MD, AGAF	2007	Xiaolu Yang, PhD
1995	Jill P. Smith, MD	2008	Sheila E. Crowe, MD, AGAF
1996	Anil K. Rustgi, MD, AGAF	2009	Mary Bronner, MD
1997	Stephen J. Meltzer, MD	2010	Jason C. Mills, MD, PhD, AGAF
1998	Juanita L. Merchant, MD, PhD	2011	Andrea Todisco, MD, AGAF
1999	Steven M. Powell, MD	2012	Adam J. Bass, MD
2000	Klaus Kaestner, PhD	2013	Yana Zavros, PhD
2001	Debra G. Silberg, MD, PhD	2014	Manuel R. Amieva, MD, PhD
2002	Steven F. Moss, MD, AGAF	2015	Linda C. Samuelson, PhD
2003	Lopa Mishra, MD	2016	Richard J. DiPaolo, PhD
2004	James R. Goldenring, MD, PhD, AGAF	2017	Zhibin Chen, MD, PhD

AGA Institute

AGA Gastric Cancer Research Award

Use the AGA Clinical Guidelines app to participate in MACRA

In 2017, eligible clinicians can use the AGA Clinical Guidelines app — through attestation of its use — to meet your 2017 CMS Merit-based Incentive Payment System (MIPS) pick your pace requirements as one way to try to avoid a payment penalty in 2019. The AGA Clinical Guidelines app has also been proposed by CMS as a 2018 Improvement Activity under MIPS.

How do you attest for 2017?
First, search for and download the AGA Clinical Guidelines app via the Apple App Store or Google Play.

After actively using the AGA Clinical Guidelines app, you will be able, in the near future, to go to the CMS Enterprise Portal to attest that you have met the 2017 MIPS improvement activity participation requirement. AGA will let you know when the portal opens.

CMS lowered the cost performance category to 0% in the 2017 pick your pace year and gave clinicians three reporting options under MIPS:

- **Option one:** Report to MIPS for a full 90-day period or full year on quality, improvement activities, and advancing care information and maximize the chance to qualify for positive payment adjustments.
- **Option two:** Report less than a year but for the full 90-day period on one quality measure, more than one improvement activity, or more than the required measures in advancing care information to avoid penalties and to receive a possible positive update.
- **Option three:** Report one quality measure, one improvement activity, or measures of advancing care information to avoid penalty.

Advanced Alternative Payment Models are another way to participate in MACRA in 2017.

What are improvement activities?
The MIPS pathway under the Medicare Access and CHIP Reauthorization Act (MACRA) uses quality and cost data to determine your payment, and replaces the previous framework that included the Medicare EHR Incentive Program, the Physician Quality Reporting System and the Value-Based Payment Modifier program. Physicians participating in MIPS will be scored on four categories:

- Quality.
- Advancing care information.
- Improvement activities.
- Cost.

The AGA Clinical Guidelines app is one way to satisfy participation in the improvement activities category.

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Honor a family member, friend, or colleague while supporting the work of our mission through a gift to the AGA Research Foundation. Your gift will honor a loved one or yourself and support the AGA Research Awards Program, while giving you a tax benefit. The AGA Research Awards Program recruits, retains, and supports the most promising investigators in gastroenterology and hepatology.

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- **A gift through your will or living trust.** You can include a bequest in your will or living trust stating that a specific asset, certain dollar amount, or more commonly a percentage of your estate will pass to the AGA Research Foundation at your death in honor of your loved one.

Your gift directly supports the talented young researchers working to advance our understanding of digestive diseases. Make a tax-deductible donation to help spur innovation. Donate today at www.gastro.org/donateonline.

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For first-line constipation therapy, stick with the leader

The AGA recommends PEG laxatives (like MiraLAX) as a first-line constipation treatment[1]

- ✔ 96% patient satisfaction rate*
- ✔ #1 GI-recommended laxative for over 10 years

Start with MiraLAX for proven relief of occasional constipation.

MiraLAX®
Polyethylene Glycol 3350, Powder for Solution, Osmotic Laxative

Doctor recommended, patient approved

*Survey of 300 consumers, 2017.

Use as directed on product labeling or as directed by your doctor.

Reference: 1. Clinical decision support tools. American Gastroenterological Association website. http://campaigns.gastro.org/algorithms/constipation/index.html. Accessed May 12, 2017.

PERSPECTIVE

Do direct-acting antivirals benefit or harm patients with hepatitis C?

The availability of direct-acting antivirals (DAAs) has revolutionized treatment of hepatitis C. Sustained virologic response (SVR) can be routinely achieved in more than 95% of patients – except in those with decompensated cirrhosis – with a 12-week course of these oral drugs, which have minimal adverse effects. Thus, guidelines recommend that all patients with hepatitis C should be treated with DAAs.[1] It was a shock to the medical community when the recent Cochrane review concluded there was insufficient evidence to confirm or reject an effect of DAA therapy on HCV-related morbidity or all-cause mortality.[2] The authors cautioned that the lack of valid evidence for DAAs' effectiveness and the possibility of potential harm should be considered before treating people with hepatitis C with DAAs. Their conclusion was in part based on their rejection of SVR as a valid surrogate for clinical outcome. Previous studies of interferon-based therapies showed that SVR was associated with improvement in liver histology, decreased risk of hepatocellular carcinoma (HCC), and mortality.

DAAs have only been available for a few years, yet increasingly, data show that SVR achieved with DAAs has beneficial effects similar to those seen with interferon-based therapies. The most dramatic benefit is observed in patients with decompensated cirrhosis, in whom improvement in liver function and reversal of cirrhosis complications can occur within a few months of treatment, allowing some of these patients to be taken off the transplant waiting list.[3] A potential concern for harm was raised by several studies suggesting DAAs may increase the risk of HCC, but these studies involved small numbers of patients. The recent study by Kanwal et al. with 22,500 patients treated with DAAs showed the incidence of HCC in patients who achieved SVR after DAA therapy was 72% lower than those who did not achieve SVR.[4] They also found that patients treated in the DAA era were older and more likely to have cirrhosis and comorbidities that increase the risk of HCC, compared with those treated in the interferon era, highlighting the pitfalls of comparison with historical data. This large study did not find any evidence of harm but rather benefits of DAAs and support for early, rather than late, initiation of treatment.

Treatment of hepatitis C with DAAs represents one out of a handful of cases in which we can claim that a cure for a chronic disease is possible; however, treatment must be initiated early before advanced fibrosis or cirrhosis to prevent a persistent, though greatly reduced, risk of HCC. Physicians managing patients with hepatitis C should make treatment decisions based on evidence from the entire literature – which supports claims of the DAA treatment's benefits and refutes allegations of its harmfulness – and should not be swayed by the misguided conclusions of the Cochrane review.

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Anna S. Lok, MD, AGAF, FAASLD, is the Alice Lohrman Andrews Research Professor in Hepatology in the department of internal medicine at the University of Michigan Health System in Ann Arbor. She has received research grants from Bristol-Myers Squibb and Gilead through the University of Michigan.

SVR is key to reduced morbidity

Liver Cancer *from page 1*

patients," wrote Fasiha Kanwal, MD, from the Michael E. DeBakey Veterans Affairs Medical Center in Houston and her coauthors. "Although a few recent studies have raised concerns that DAA might accelerate the risk of HCC in some patients early in the course of treatment, we did not find any factors that differentiated patients with HCC that developed during DAA treatment."

'Delaying treatment until patients progress to cirrhosis might be associated with substantial downstream costs incurred as part of lifelong HCC surveillance and/or management of HCC.'

The results highlighted the importance of early treatment with antivirals, beginning well before the patients showed signs of progressing to advanced fibrosis or cirrhosis, the investigators noted.

"Delaying treatment until patients progress to cirrhosis might be associated with substantial downstream costs incurred as part of lifelong HCC surveillance and/or management of HCC," they wrote.

Sustained virologic response to DAAs also was associated with a longer time to diagnosis, and patients who didn't achieve it showed higher rates of cancer much earlier. The most common antivirals used were sofosbuvir (75.2%; 51.1% in combination with ledipasvir), the combination of paritaprevir/ritonavir (23.3%), daclatasvir-based treatments (0.8%), and simeprevir (0.7%).

While the patients achieved SVR that showed similarly beneficial effects on HCC risk in patients with or without cirrhosis, the authors also noted that patients with cirrhosis had a nearly fivefold greater risk of developing cancer than did those without (HR, 4.73; 95% CI, 3.34-6.68). Similarly, patients with a fibrosis score (FIB-4) greater than 3.25 had a sixfold higher risk of HCC, compared with those with a value of 1.45 or lower.

Researchers commented that, at this level of risk, surveillance for HCC in these patients may be cost effective.

"Based on these data, HCC surveillance or risk modification may be needed for all patients who have progressed to cirrhosis or advanced fibrosis (as indicated by high FIB-4) at the time of SVR," they wrote.

Alcohol use was also associated with a significantly higher annual incidence of HCC (HR, 1.56; 95% CI, 1.11-2.18).

Among the study cohort, 39% had cirrhosis, 29.7% had advanced fibrosis, and nearly one-quarter had previously been treated for hepatitis C infection. More than 40% also had diabetes, 61.4% reported alcohol use, and 54.2% had a history of drug use.

"DAAs offer a chance of cure for all patients with HCV, including patients with advanced cirrhosis, older patients, and those with alcohol use – all characteristics independently associated with risk of HCC in HCV," the authors explained. "These data show the treated population has changed significantly in the DAA era to include many patients with other HCC risk factors; these differences likely explain why the newer cohorts of DAA-treated patients face higher absolute HCC risk than expected, based on historic data."

The study was partly supported by the Department of Veteran Affairs' Center for Innovations in Quality, Effectiveness, and Safety at the Michael E. DeBakey VA Medical Center. No conflicts of interest were declared.

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Environment affects microbiome

Urban *from page 1*

gastroenterologist at Children's Hospital of Eastern Ontario, Ottawa, and his coinvestigators. "These findings demonstrate the importance of early life exposure in altering the risk of IBD, the greater magnitude of effect of this environmental risk factor on the risk of childhood-onset disease, and the importance of adequately defining rurality."

The retrospective, population-based study gathered a total of 45,567 IBD patients: 6,662 living in rural residences and 38,905 living in urban residences in Nova Scotia, Ontario, Alberta, and Manitoba, Canada.

'The mechanism by which rurality protects against IBD is uncertain, and may include dietary and lifestyle factors, environmental exposures, or segregation of individuals with different genetic risk profiles.'

Patients in rural areas were on average older than urban patients (average age, 43 years vs. 40 years). Rural patients were also, on average, diagnosed later than were urban patients, with an average age at diagnosis of 42 years, compared with 38 years for urban residents.

The IBD incidence rate among urban patients was 33.16/100,000 (95% CI, 27.24-39.08), compared with 30.72/100,000 (95% CI, 23.81-37.64) among rural residents (Am J Gastroenterol. 2017 Jul 25. doi: 10.1038/ajg.2017.208).

Exposure to these environments while growing up was especially significant, with the lowest rate among children younger than 10 years in rural areas (incidence rate ratio, 0.58; 95% CI, 0.43-0.73), followed by adolescents between 10 and 17.9 years (IRR, 0.72; 95% CI, 0.64-0.81), according to investigators.

The incidence rate of IBD among rural children stayed consistent from birth through age 5 years, which may be evidence that development of IBD later in life is correlated with patients' time in rural areas, the investigators reported.

Although Dr. Benchimol and his coauthors could not point to the exact reason for these results, they said factors such as diet and early exposure to animals, which may help develop useful bacteria that could help fight IBD development, are possible explanations.

"The mechanism by which rurality protects against IBD is uncertain, and may include dietary and lifestyle factors, environmental exposures, or segregation of individuals with different genetic risk profiles," the investigators wrote.

"These effects may be stronger in children because their gut microbiome is in evolution and may be vulnerable to changes in the first 2 years of life."

This study was limited by certain classification factors, such as what constitutes an urban or rural area, which may have affected the outcomes. A lack of information on the effects of confounding factors, particularly ethnicity, genotype, phenotype, disease severity, or family history also limited this study, the investigators said.

The Janssen Future Leaders in IBD Program funded the study. Investigators reported receiving financial support from or holding leadership positions in the Canadian Institutes of Health Research, the Canadian Child Health Clinician Scientist program, and the Nova Scotia Health Research Foundation.

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Safety alert for intragastric balloon systems

BY LORI LAUBACH
Frontline Medical News

The Food and Drug Administration announced a safety alert on Aug. 10, 2017, for liquid-filled intragastric balloon systems, as they have caused five reports of unanticipated deaths that occurred from 2016 to present in patients.

The cause or incidence of patient death is still unknown, and the FDA has not been able to definitively attribute the deaths to the devices or the insertion procedures for these devices. All five reports show that patient deaths occurred within a month or less of balloon placement. In three of the reports, death occurred as soon as 1-3 days after balloon placement. The FDA has also received two additional reports of deaths in the same time period related to potential complications associated with balloon treatment.

In February 2017, the FDA issued a letter to health care providers to recommend close monitoring of patients with liquid-filled intragastric balloon systems used to treat obesity for the potential risks of acute pancreatitis and spontaneous overinflation. Since then, the product labeling to address these risks has been revised.

The FDA continues to recommend that health care providers closely monitor patients treated with these devices for complications. Any adverse events related to intragastric balloon systems should be reported through MedWatch. The FDA will keep the public informed as new information becomes available.

Read the full safety alert on the FDA's website.

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PERSPECTIVE

Be careful, but reserve judgment for now

As past chair of the AGA Center for GI Innovation and Technology, I have been closely following balloon-based obesity devices as they've entered the marketplace. The center has welcomed the introduction of these noninvasive devices that can be managed by GIs, and we've worked closely with device companies and the FDA for the past several years to ensure these devices were introduced to the market in a safe and efficient manner.

The FDA's recent safety communication about the potential risks related to these devices is concerning, but it is not fully evaluated as to causation. The FDA report states: "At this time, we do not know the root cause or incidence rate of patient death, nor have we been able to definitively attribute the deaths to the devices or the insertion procedures for these devices (e.g., gastric and esophageal perforation, or intestinal obstruction)."

We do not have enough information now to connect these recent patient deaths to these devices. That said, the FDA's letter reinforces a few important points. Foremost, the fact that complications and adverse events can occur with any procedure. For physicians using intragastric balloons, each patient must be appropriately evaluated prior to the decision to place the balloon, especially for the potential risks of anesthesia and an endoscopic procedure. Patients must be monitored closely during the entire term of treatment, and following the procedure, in order to detect the development of possible complications, and each patient should be instructed to contact his or her physician immediately upon the onset of any unexpected symptoms.

Michael Kochman MD, AGAF, is the Wilmott Family Professor of Medicine, professor of medicine in surgery, gastroenterology division, University of Pennsylvania, Philadelphia.

Fujifilm issues recall to update ED-530XT duodenoscopes

BY LUCAS FRANKI
Frontline Medical News

Fujifilm has issued an Urgent Medical Device Correction and Removal notification for all ED-530XT duodenoscopes, according to a Safety Alert from the Food and Drug Administration.

The recall, initiated voluntarily by Fujifilm, includes replacement of the ED-530XT forceps elevator mechanism including the O-ring seal, replacement of the distal end cap, and new operation manuals.

The FDA recommends that all health care providers acknowledge Fujifilm's notification and identify any affected products and be aware of the reprocessing procedure found in the FDA's December 2015 Safety Communication regarding the Fujifilm duodenoscope. When new operation manuals are received, old manuals should be removed and destroyed properly.

"Reprocessing is a detailed, multistep process to clean and disinfect or sterilize reusable devices."

Find the full Safety Alert on the FDA website.

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DDSEP eight Digestive Diseases Self-Education Program

Quick quiz answers

Q1: Answer D

Objective: Identify the clinical presentation and risk factors for small intestinal bacterial overgrowth.

Rationale: This patient likely has small intestinal bacterial overgrowth (SIBO) based on her symptoms, the steatorrhea with the positive Sudan stain for fat, and a slight anemia with an elevated MCV suggestive of vitamin B_{12} deficiency secondary to the bacterial overgrowth. She also has scleroderma, a condition commonly associated with SIBO, because it impairs gastrointestinal motility.

While hydrogen breath testing may help establish the diagnosis of SIBO, there is variable sensitivity and specificity of the testing with false-positive and false-negative test results frequently occurring. An alternative strategy is to treat empirically with an accepted antibiotic regimen and assess response after the course is completed.

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Q2: Answer B

Objective: Recognize the clinical presentation and imaging features of main duct intraductal papillary mucinous neoplasm (IPMN)

Critique: The patient's imaging is consistent with main duct IPMN and the mild pancreatitis is likely a consequence of mucin plugging and obstruction. Main duct IPMN is associated with a higher incidence of malignancy, compared with branch duct IPMN and surgical resection is recommended if the patient is a surgical candidate.

While further sampling with endoscopic ultrasound or endoscopic retrograde cholangiopancreatography may be helpful, these tests have a low sensitivity for identifying dysplasia and are unlikely to change management. Surveillance with MRI would be appropriate if the patient does not wish to undergo surgery at this time.

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Therapeutic drug monitoring in IBD

BY AMY KARON
Frontline Medical News

Physicians should perform reactive therapeutic drug monitoring to guide changes in anti–tumor necrosis factor (TNF) therapy in patients with active inflammatory bowel disease and should consider target trough concentrations of at least 5 mcg/mL for infliximab, at least 7.5 mcg/mL for adalimumab, and at least 20 mcg/mL for certolizumab pegol, according to a guideline from the AGA Institute, published in the September 2017 issue of Gastroenterology (doi: 10.1053/j.gastro.2017.07.032).

However, only low-quality evidence supports this and other guideline recommendations, wrote Joseph D. Feuerstein, MD, of Beth Israel Deaconness Medical Center in Boston and his associates from the AGA Clinical Guidelines Committee. For example, the only randomized controlled trial (Gut. 2014 Jun;63[6]:919-27) on reactive therapeutic drug monitoring (TDM) of an anti-TNF agent set the target trough concentration for infliximab at 0.5 mcg/mL or more, 10-fold lower than what current evidence supports. The trial found no significant difference between 12-week rates of remission in the TDM and empiric dose escalation arms. Observational studies suffered from imprecision and flawed designs, and none addressed TDM in clinically remitted patients with active endoscopic disease. "As treatment paradigms shift toward targeting mucosal healing, indirect evidence suggests that using reactive TDM in this situation would be reasonable," the authors wrote. "However, optimal target trough concentrations for achieving mucosal healing are uncertain and may be higher than those suggested for achieving clinical remission."

Therapeutic drug monitoring can help guide whether to ramp up a dose (if the trough level is below the threshold) or switch therapy (if the trough level is above the threshold) when patients are not responding adequately to maintenance treatment. A nonresponder with optimal trough concentrations might need to switch drug classes, the guideline noted. A patient with low trough levels and no antidrug antibodies is probably experiencing rapid drug clearance in the setting of high inflammation. A patient with low or undetectable trough levels and high antidrug antibody titers has developed neutralizing antidrug antibodies. However, trough concentrations can vary for many other reasons, ranging from disease severity and inflammation to body mass index and sex. Therefore, target levels also vary and can be challenging to set.

The AGA makes no recommendation about routine, proactive TDM in patients with quiescent IBD who are on anti-TNF agents. While proactive TDM can shed light on endoscopic response and drug clearance, it might also trigger a premature switch of

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THIS PRESENTATION WAS GIVEN AT DIGESTIVE DISEASE WEEK® 2017

Navigating the complex landscape of IBD therapies

BY EDWARD V. LOFTUS JR., MD, AGAF

I provided an update on existing, new, and upcoming medical therapies for Crohn's disease (CD) and ulcerative colitis (UC), with a focus on studies presented at Digestive Disease Week® 2017.

In one study of over 13,000 inflammatory bowel disease (IBD) patients in Medicare/Medicaid databases, it was found that among those treated with corticosteroids in the previous year, patients started on a tumor necrosis factor (TNF) inhibitor within the next year had mortality rates that were at least 22% lower than those of patients treated with prolonged corticosteroids over the next 12 months (Gastroenterology. 2017;152[5 Suppl 1]:S65-5). Initial results of the CALM study were presented, comparing a treat-to-target (T2T) algorithmic medical escalation approach in moderate to severe CD to a more conventional approach. Medical therapy was primarily adalimumab based and was escalated based on "success criteria," which included not only symptomatic remission but also normalization of serum C-reactive protein and fecal calprotectin. At week 48, the rate of endoscopic remission was significantly higher (45.9%) in the T2T group than in conventionally managed patients (30.3%, *P* = .01), thus demonstrating the superiority of a T2T approach (Gastroenterology 2017;152[5 Suppl 1]:S155).

After several years of discussing the advent of biosimilars, one has arrived in the United States, infliximab-dyyb (Inflectra®, Pfizer). This molecule was approved on the basis of a phase 3 trial in rheumatoid arthritis and a pharmacokinetic trial in psoriasis, and approval was extrapolated to most approved indications including IBD. Concerns had been raised that, despite the rigorous approval process, there might be subtle differences in biosimilars leading to suboptimal efficacy or to less favorable safety. A phase 3 trial of infliximab-dyyb in moderate to severe CD showed practically identical efficacy and safety compared with originator infliximab (Gastroenterology. 2017;152[5 Suppl 1]:S65). Another study compared switching from originator to infliximab-dyyb to continuation of originator infliximab among patients with a variety of conditions including IBD, and overall, there were no significant differences in clinical worsening between the "switchers" and those continued on the originator compound (Gastroenterology. 2017;152[5 Suppl 1]:S65-6).

Dr. Edward V. Loftus Jr.

Ustekinumab is a monoclonal antibody to interleukins 12 and 23, and was approved for moderate to severe CD last year on the basis of the pivotal UNITI-1, UNITI-2, and IM-UNITI trials (N Engl J Med. 2016;375:1946-60). A weight-based intravenous loading dose was shown to be effective at inducing clinical response in both patients who had failed or were intolerant to anti-TNF therapy and those who had not. The responders in both induction trials were randomized to two subcutaneous doses of ustekinumab or placebo, and at the end of the 44-week trial, the drug met multiple efficacy endpoints, including clinical remission, clinical response, steroid-free remission, and sustained clinical remission. In another abstract, the rate of tuberculosis reactivation within the clinical development program of ustekinumab across all indications (6,581 patients, over 12,000 patient-years of follow-up) was significantly lower at 0.02 cases per 100 patient-years, compared with the rates seen in the golimumab (0.24 per 100) and infliximab (0.39 per 100) development programs (Gastroenterology. 2017;152[5 Suppl 1]:S596), illustrating that the safety profile of ustekinumab may be significantly different from that of anti-TNF agents.

Tofacitinib, which inhibits mainly JAK1 and JAK3 receptors, is an emergent oral small mol-

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therapies; this is particularly likely because physicians have sparse data on either target trough levels for asymptomatic patients or the clinical significance of "low-titer" antidrug antibodies. The optimal frequency of proactive TDM also remains unclear.

Pending better data, the AGA recommended checking infliximab or adalimumab trough levels as close to the next dose as possible – that is, within 24 hours. Drug trough levels are consistent across commercial assays, but antidrug antibody titers are not, and there are no uniform thresholds for clinically relevant antidrug antibody titers. "Therefore, it may be beneficial to utilize the same assay when checking for trough concentration and antidrug antibodies," the guideline stated.

For patients on a thiopurine, routine testing of thiopurine methyltransferase (TPMT) enzyme or genotype is recommended to guide dosing. In three pooled studies comprising 1,145 patients, only two patients were homozygous; further, rates of hematologic adverse events, clinical remission, and treatment discontinuation did not differ based on TPMT testing itself. However, using TPMT testing to guide dosing was associated with an 89% decrease in the risk of hematologic adverse events among patients who had a homozygous genotype or had low or absent TPMT enzymatic activity. "While this risk may be mitigated by routine laboratory CBC checking, adherence to regular monitoring in clinical practice is suboptimal," the guideline stated. "It is important to continue to perform routine lab monitoring [of] CBC and liver enzymes after starting a thiopurine."

A nonresponder with optimal trough concentrations might need to switch drug classes. A patient with low trough levels and no antidrug antibodies shows rapid drug clearance.

The AGA also conditionally supported reactive monitoring of thiopurine metabolites to guide treatment changes if patients develop breakthrough symptoms or treatment-related adverse effects. For active IBD symptoms in spite of thiopurine monotherapy, a target 6-thioguanine cutoff between 230 and 450 pmol per 8 x 10^8 RBC is recommended. Again, supporting evidence is of "very low quality" – in a retrospective, observational study, patients who received treatment according to a TDM algorithm were five times more likely to respond to a change in therapy (relative risk, 5.2). The guideline recommended against monitoring thiopurine metabolites in quiescent IBD. Studies did not support this practice, compared with standard dosing, although no study of thiopurine metabolites included patients on thiopurine/anti-TNF combination therapy, the guideline's authors noted.

The guideline includes clinical decision support tools on when to perform TDM and how to interpret results when patients are taking an anti-TNF agent or a thiopurine. The guideline does not cover vedolizumab or ustekinumab because data are sparse. Other knowledge gaps include when best to measure trough concentrations; whether empiric dose escalation or TDM is preferred if response to induction is suboptimal; how target trough concentrations vary based on disease phenotype, disease state, or treatment goals; which levels and durations of antidrug antibody titers are clinically significant; and whether to suppress antidrug antibodies before changing therapy. Future studies should compare routine proactive and reactive TDM, investigate how often to perform proactive TDM, and characterize TDM of newly approved biologic agents, the guideline concluded.

The authors of the guideline document disclosed no conflicts related to the guideline topic.

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ecule drug for UC. Three phase 3 randomized placebo-controlled trials (OCTAVE-1, OCTAVE-2, and OCTAVE Sustain) of tofacitinib treatment in moderately to severely active UC patients have been recently published (N Engl J Med. 2017;376:1723-36). The rates of clinical remission at week 8 were significantly greater in patients who were treated with 10 mg tofacitinib than placebo in both induction trials, and results were similar regardless of anti-TNF exposure status. Clinical responders in the induction studies were randomized to placebo or two doses of tofacitinib. At week 52, remission rates were significantly higher in the patients treated with 10 mg tofacitinib twice daily and 5 mg tofacitinib twice daily than those receiving placebo. The percentages of tofacitinib-treated patients who achieved mucosal healing were significantly greater than those in the placebo group. Serious infections occurred significantly more frequently in the tofacitinib than placebo group during induction, but not during maintenance. However, rates of herpes zoster were higher with maintenance therapy at 10 mg twice daily (5.1%) than with placebo (0.5%).

A recently published phase 2 study of filgotinib, a selective JAK1 inhibitor, reported that the remission rate at week 10 was significantly higher in active CD patients receiving 200 mg of filgotinib daily than in those receiving placebo (Lancet. 2017;389:266-75). A phase 2 trial of another selective JAK1 inhibitor, upadacitinib (ABT-494), for induction therapy in CD patients with a history of failure or intolerance to TNF-antagonists, was presented at DDW (Gastroenterology. 2017;152[5 Suppl 1]:S1308-9). Higher rates of clinical remission at week 16 were seen in patients on 6 mg upadacitinib twice daily than on placebo, and several doses of upadacitinib were significantly better than placebo for inducing endoscopic remission at week 12 or 16. Serious adverse events were seen in 9%-15% of CD patients treated with these two agents (vs. 4%-5% in placebo-treated patients).

Smad7 regulates the signaling of transforming growth factor (TGF)-beta1, an anti-inflammatory cytokine. Mongersen is an orally delivered anti-sense oligonucleotide that inhibits Smad7 and restores TGF-beta1 signaling, and is being developed for CD. The efficacy of induction therapy for active CD patients with limited active disease (terminal ileum or proximal colon) was demonstrated in a phase 2 study (N Engl J Med. 2015;372:1104-13). Interestingly, this study showed significantly higher rates of clinical remission at day 15 with mongersen. However, there were no endoscopic data available in this trial; baseline serum C-reactive protein concentrations were low and did not decrease significantly. This drug appears to be well tolerated, and serious adverse events were not significantly higher than for placebo. In a phase 1b study, correlations between clinical and endoscopic outcomes were explored, and among 52 CD patients, SES-CD reductions of at least 25% at week 12 were seen in 37% of mongersen-treated patients (Gastroenterology. 2017;152[5 Suppl 1]:S198).

In summary, the future of IBD medical therapy is bright due to the recent introduction of therapies with novel mechanisms of action and favorable safety profiles (e.g., vedolizumab and ustekinumab), potentially lower-cost biosimilars, and multiple compounds in the drug development pipeline.

Dr. Loftus is professor of medicine, Mayo Clinic College of Medicine, director of the Inflammatory Bowel Disease Interest Group, the division of gastroenterology and hepatology, Rochester, Minn.

The full scope of GI advances

BY SUZANNE ROSE, MD, MSED, AGAF

What distinguished this year's course offering was the overall approach and philosophy to utilize educational processes and educational theory resulting in an educational program that adhered to the AGA's commitment to high-quality, evidence-based, and theory-driven programming.

As a first step in planning the course, we performed a needs assessment. By identifying what learners need to know, we endeavored to develop the ideal course. Our course directors, supported by the AGA staff, reviewed past course evaluations, and in particular, the comments related to suggestions for future programs. We also reviewed and discussed with experts the emerging trend topics and need-to-know areas in GI and hepatology. In doing so, an outline of topics was created, which was subsequently approved by AGA Institute's Education and Training Committee.

The next step was to require that every learning activity identify its objectives, in behavioral terms, so that postcourse assessments could determine if the objectives were met. While all speakers were required to provide objectives for their specific talks, the following represent the overall objectives of the course on which the course curriculum was based.

Objectives

At the completion of this course the attendee will be able to:

1. Identify new strategies in the evaluation and management of GI and hepatobiliary problems
2. Recognize medical, surgical, and technological advances in the field of GI and hepatology
3. Apply new strategies for evaluation, therapeutic options, and technology to the optimal care of patients

It is challenging to craft large audience educational experiences so that they also address adult learning principles. We know that adult learners benefit from experiences that are relevant, are problem-centered (rather than content oriented), promote active learning, and provide feedback to the learner. We therefore requested that each session begin with a brief case. Having clinical examples helps learners frame the disease process, and can help demonstrate the importance of learning the material. Finally, all participants were given the opportunity to review each session, and the course in its entirety, to help us improve future programming.

Lunch sessions promoted active learning with the opportunity for interaction, and we also included case-based breakout sessions. Not only was CME accreditation provided, but Maintenance of Certification (MOC) credit was also available.

This educational offering provided a setting to hear from leaders in GI and hepatology, and for learners to gain new insights to take home and apply to the care of patients. The sections that follow provide brief summaries of the sessions from the course written by the moderators.

Please visit http://pgcourse.gastro.org/home to access the content from DDW.

Dr. Rose is a professor of medicine, the Senior Associate Dean for Education, University of Connecticut School of Medicine, Farmington, and the 2017 AGA Postgraduate Course Director.

All guts and glory – esophagus, stomach, small intestine

BY STUART J. SPECHLER, MD, AGAF

Prakash Gyawali, MD, led off the session with a lecture on functional heartburn, which he defined as burning retrosternal discomfort not relieved by antisecretory therapy, in a patient for whom endoscopy, esophageal pH monitoring, and manometry have revealed no evidence of gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE), or major esophageal motility disorders. When performing pH monitoring to assess for functional heartburn, Dr. Gyawali advised that the test be done with patients off of proton pump inhibitors (PPIs). Despite similarity to the heartburn sensation of GERD, Dr. Gyawali pointed out how functional heartburn has features resembling irritable bowel syndrome, such as its association with anxiety and depression, and its response to neuromodulators (e.g., antidepressants). He discussed how new impedance-based esophageal metrics such as the postswallow-induced peristaltic wave index and measurement of mean nocturnal baseline impedance might be used to confirm a diagnosis of functional heartburn. Although neuromodulators remain the mainstay of management for functional heartburn, Dr. Gyawali discussed encouraging preliminary results of studies on psychotherapy, hypnotherapy, and alternative therapies such as acupuncture.

Rhonda Souza, MD, AGAF, discussed EoE, focusing especially on the controversial condition of PPI-responsive esophageal eosinophilia (PPI-REE) in which patients have typical EoE symptoms and histology, with no evidence of GERD by endoscopy or esophageal pH monitoring, yet they respond to PPI therapy. She discussed two possible explanations for PPI-REE: 1) the patients have subclinical GERD that responds to PPI antisecretory effects, or 2) the patients have EoE that responds to PPI anti-inflammatory effects. Dr. Souza reviewed data from her laboratory showing that omeprazole can block the secretion of eotaxin-3, a potent eosinophil chemoattractant in esophageal epithelial cells stimulated with allergic (Th2) cytokines in vitro. This potential anti-inflammatory PPI effect is entirely independent of any effect on gastric acid inhibition. After reviewing recent clinical and esophageal transcriptome data, Dr. Souza concluded that PPI-REE is probably just a subset of EoE, not an independent disorder.


DR. SPECHLER

John Inadomi, MD, AGAF, discussed Barrett's esophagus and esophageal adenocarcinoma. He pointed out the inadequacy of current screening programs, noting studies showing that less than 10% of patients found to have esophageal adenocarcinoma had a prior diagnosis of Barrett's esophagus. He estimated the annual incidence of adenocarcinoma at 0.12%-0.5% for patients with nondysplastic Barrett's metaplasia. He discussed how current American College of Gastroenterology guidelines call for screening men who have chronic GERD symptoms with at least two other Barrett's cancer risk factors (age greater than 50 years, white race, central obesity, cigarette smoking, family history of Barrett's esophagus), and noted how the very low risk of esophageal adenocarcinoma in women (similar to the risk of breast cancer in men) supports the ACG recommendation not to screen women routinely for Barrett's esophagus. Dr. Inadomi recommended endoscopic eradication as the preferred treatment for patients with confirmed dysplasia of any grade. He also noted that the removal of nodular lesions by endoscopic mucosal resection or endoscopic submucosal dissection is a crucial part of endoscopic eradication therapy.

In a lecture titled "The truth about PPIs," Byron Cryer, MD, reviewed a number of potential adverse effects of PPIs, including *Clostridium difficile*–associated diarrhea, bone fractures, kidney disease, dementia, myocardial infarction, and interactions with clopidogrel. He pointed out that most of these putative adverse effects have been identified as modest increases in risks noted in observational studies, and the quality of this evidence is considered low or very low. In contrast, the benefits of PPIs for patients with complicated GERD and for patients at risk for NSAID complications have been established in high-quality, randomized controlled trials. Dr. Cryer concluded that, when PPIs are prescribed appropriately, their benefits likely outweigh their risks. However, he also noted that PPIs frequently are prescribed inappropriately, in which case they have no benefit and their potential for risk assumes greater importance.

Sheila Crowe, MD, AGAF, delivered the last lecture of the session, discussing celiac disease and gluten sensitivity. She reviewed recent data suggesting a role for infection with reovirus in triggering the development of celiac disease, and she noted that tissue transglutaminase IgA remains the best test to screen for the condition. She discussed the controversial topic of nonceliac gluten sensitivity, in which patients report symptoms or health alterations that they perceive to be the result of gluten ingestion. She pointed out difficulties in establishing an unequivocal diagnosis of nonceliac gluten sensitivity and, for patients without celiac disease, she highlighted a number of potential drawbacks of a gluten-free diet, including its expense, higher fat and sugar content, and increased levels of toxic metals such as arsenic and mercury.

Dr. Spechler is chief of the division of gastroenterology and co-director of the Center for Esophageal Diseases, Baylor University Medical Center at Dallas; he is an investigator/professor and co-director of the Center for Esophageal Research, Baylor Scott and White Research Institute, Dallas.

The biliary tree and pancreas: An overview

BY MICHELLE K. KIM, MD, MSC, AGAF

The session titled "The biliary tree and pancreas" provided an overview of the most important pancreaticobiliary diseases, allowing experts to delineate their approaches to challenging aspects of these conditions.

Timothy Gardner, MD, MS, focused on the management and treatment of sequelae in patients with acute pancreatitis. He provided support for the use of lactated Ringer's as the fluid of choice, cautioning against over-resuscitation. He advised early oral feeds, without clear preference for nasogastric or nasojejunal administration. Dr. Gardner emphasized the importance of classifying type of fluid collection to optimize clinical decision making. Endoscopic techniques appear to be safer and as efficacious as surgical approaches. Regarding thrombosis, anticoagulation was recommended unless an absolute contraindication exists. He also recommended addressing symptomatic ductal disruptions.


DR. KIM

Matthew J. DiMagno, MD, AGAF, provided important insights into chronic pancreatitis. He first advised classifying patients with recurrent attacks of pancreatitis. Also, pain patterns in chronic pancreatitis may be categorized into two groups: short, intermittent pain (type A) and constant pain (type B). The former can often be managed without invasive procedures, while the latter is often managed with interventions. When addressing the pain of chronic pancreatitis, clinicians need to establish the diagnosis, advise abstinence from alcohol and smoking, and advocate adequate nutrition and other treatments. The approach to constant pain requires exclusion of anatomic pathology and appropriate treatment of neuropathic and centralized pain. Assessment of duct morphology also impacts treatments; patients with dilated or large duct disease should undergo drainage procedures.

Douglas Adler, MD, AGAF, provided pointers on distinguishing between malignant and benign biliary strictures. Ruling out a malignant stricture entails use of multiple diagnostic modalities to image and to sample abnormalities, such as a dominant stricture in primary sclerosing cholangitis. Fluorescence in situ hybridization (FISH) and cholangioscopy are fairly widely used, while other techniques such as confocal laser endomicroscopy are used less frequently. Benign biliary strictures occur frequently in the liver transplant population, both anastomotic and nonanastomotic. Benign biliary strictures may also occur in chronic pancreatitis;

Continued on following page

Hot topics in 2017

BY UMA MAHADEVAN, MD, AGAF

The 2017 Postgraduate Course started out with four hot topics that dominated the year – opioid dependence, a cure for hepatitis C, and understanding and then manipulating the microbiome. From David Dickerson, MD, we learned that abdominal pain is complex and with an evolving classification scheme. Ignoring the biopsychosocial aspects and origins of pain is a sure way to lead to addiction and "pain behavior." He reviewed the opioid guidelines that involve a comprehensive approach to therapy – setting functional goals, assessing the risks and benefits, and using the lowest necessary doses of short-acting agents for a defined period of time and then reassessing. In patients with chronic pain and opioid dependence, the gastroenterologist should seek the help of a chronic pain specialist. We should also refer for nonpharmacologic therapy such as cognitive behavioral therapy and biofeedback.

From there, Octavia Pickett-Blakely MD, MHS, took us through the role of the microbiome in obesity (wouldn't it be great to take probiotics or an annual fecal microbial transplant [FMT] to keep our weight under control?). She discussed the likely link between obesity and antibiotic use in early childhood and the different gut microbiota compositions in the obese and lean. Altered gut microbiota can affect energy homeostasis, which can then lead to obesity. She discussed the potential role of breastfeeding, low-fat, low-calorie, and high-fruit-vegetable-fiber diets on increasing microbial richness and reducing obesity. While diet and a sedentary lifestyle remain the primary drivers of obesity, host genetics, environment, and gut permeability all play a role.

Dr. Uma Mahadevan

Norah Terrault, MD, MPH, discussed management of chronic hepatitis C (HCV) after the cure, achievable in more than 95% of patients, which has resulted in a sharp decline in listings for liver transplant. A cure is defined as undetectable HCV RNA 12 weeks after completion of therapy. So what happens next? If the patient is at risk for reinfection, they should have HCV RNA testing annually or if their liver enzymes increase. Otherwise, if their pretreatment fibrosis is low stage, no further monitoring is needed and they can follow up with their primary care provider. Intermediate-stage fibrosis should be monitored for progression. Advanced-stage fibrosis needs long-term follow-up for hepatocellular carcinoma and variceal surveillance. Modifiable risk factors, i.e., metabolic fatty liver and alcohol abuse, should be identified with appropriate counseling provided.

We went back to the microbiome for our last talk: Larry Brandt, MD, AGAF, discussed FMT for *Clostridium difficile* infection (CDI). Patients should be considered for FMT if they have more than 3 recurrences of mild to moderate CDI and failure to respond to standard therapy; more than 2 episodes of CDI resulting in hospitalization and significant morbidity; moderate CDI with no response after 1 week of standard therapy; and severe CDI with no response to standard therapy within 48 hours. Serious adverse events associated with FMT include infections and perhaps new-onset immune-mediated disease such as Sjogren's, rheumatoid arthritis, and idiopathic thrombocytopenic purpura. It is hoped that the NIH-sponsored AGA national registry for FMT will help better define outcomes and adverse events over the next 10 years.

After cure of chronic HCV infection, modifiable risk factors, i.e., metabolic fatty liver and alcohol abuse, should be identified with appropriate counseling provided.

Dr. Mahadevan is professor of clinical medicine at UCSF Medical Center, San Francisco.

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importantly, these may mimic pancreatic cancer.

During my presentation, we focused on several aspects of pancreaticobiliary neoplasia. We reviewed the multiple genetic syndromes such as Peutz-Jeghers syndrome, hereditary pancreatitis, and Lynch syndrome, all of which confer increased risk for pancreatic cancer. Endoscopic ultrasound guidance and adjunctive techniques (e.g., elastography) may improve imaging in the pancreas and improve targeting of biopsies. Needle-based confocal laser endomicroscopy is also available to provide real time cellular data, improving our ability to accurately diagnose and differentiate pancreatic cystic neoplasms. Endoscopic ultrasound–guided needle injection and other therapeutic techniques allow endoscopists to intervene therapeutically. Accurate management of pancreatic cysts depends largely on the accurate identification of mucinous cystic neoplasms. Recent guidelines delineate high-risk stigmata and worrisome features of branch-duct intraductal papillary mucinous neoplasm. We also reviewed less common neoplasms such as pancreatic neuroendocrine tumors and biliary neoplasms.

Dr. Kim is an assistant professor of gastroenterology at Mount Sinai Hospital, acting director of endoscopy, and director of endoscopic ultrasound at Mount Sinai Hospital, New York.

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PRACTICE MANAGEMENT TOOLBOX: Gastrointestinal surgery and endoscopy – recent trends in competition and collaboration

BY GYÖRGY BAFFY, MD, AGAF, AND P. MARCO FISICHELLA, MD, MBS, FACS

This article looks at the space occupied by surgery and endoscopy – how we continue to move closer to a common approach to several upper gastrointestinal problems and how the concept of a shared space dates back a generation. I have heard Peter Cotton (whom I consider a friend and colleague) speak eloquently for 25 years about how we should bridge the gap between the gastroenterologist and surgeon when we approach disorders such as gastroesophageal reflux disease, obesity, achalasia, and Barrett's dysplasia. Despite widespread agreement about this combined approach, our training, CPT codes, culture, and turf battles continue to segment our care. Caught in this cauldron is the patient, to whom we owe primary allegiance.

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

Medicine and surgery represent complementary paths for the preservation and restoration of health. Historically, medicine follows contemplative approaches to identify causative factors and uses noninvasive remedies to alter the course of disease. By contrast, the goal of surgery, aptly put by the French surgeon Ambroise Paré more than 500 years ago, is "to remove what is superfluous, to restore what has been dislocated, to separate what has grown together, to reunite what has been divided, and to redress the defects of nature." For many centuries, medicine and surgery fulfilled their respective missions with increasing success to overlapping health care constituencies through competition and collaboration. The complexity of coexisting disciplines is particularly apparent in the case of gastroenterology, a medical subspecialty fully devoted to the management of digestive diseases.

Endoscopy and the medicosurgical divide

In 1994, Peter B. Cotton, MD, a widely respected pioneer of advanced gastrointestinal endoscopy, made an emphatic plea to bridge the gap between "thinkers" and "cutters" by developing a common strategy within a new framework.[2] He noted that differences between medicine and surgery have become blurred through recent technological innovations. After more than 20 years, the medical-surgical partnership in digestive care remains challenging and Dr. Cotton's plea for enhanced collaboration between interventional gastroenterology and surgery is timelier than ever before. Although surgeons have successfully embraced laparoscopy to evolve minimally invasive abdominal interventions with reduced rates of complications, shorter hospital stay, and increased patient satisfaction, gastroenterologists developed complex and effective therapeutic endoscopy applications that erode the traditional turf of gastrointestinal surgery. However, these two fields retain their distinct protocols and their interchange remains less than optimal.

Here we consider several areas of interventional care aimed at the upper gastrointestinal tract and shared by surgery and endoscopy, finding lessons for innovators and practitioners on both sides. Endoscopy may offer less invasive and less costly solutions for the interventional management of gastroesophageal reflux disease (GERD), Barrett's dysplasia, morbid obesity, and achalasia. However, noninvasiveness and affordability are not necessarily enough to promote novel endoscopic methods in their respective fields unless they provide safe, efficient, and durable results (Figure 1). The medical-surgical middle ground is most likely to thrive through collaboration that includes integrated training, structured monitoring, and unbiased referral practices.

Dr. Baffy is an associate professor of medicine at Harvard Medical School and chief of gastroenterology at the VA Boston Healthcare System, Boston; Dr. Fisichella is associate chief of surgery at the Boston VA Healthcare System, Brigham and Women's Hospital, Harvard Medical School. The authors disclose no conflicts.

Please read the remainder of the story online at gihepnews.com under Practice Management or at the Clinical Gastroenterology and Hepatology website: http://dx.doi.org/10.1016/j.cgh.2017.02.014.

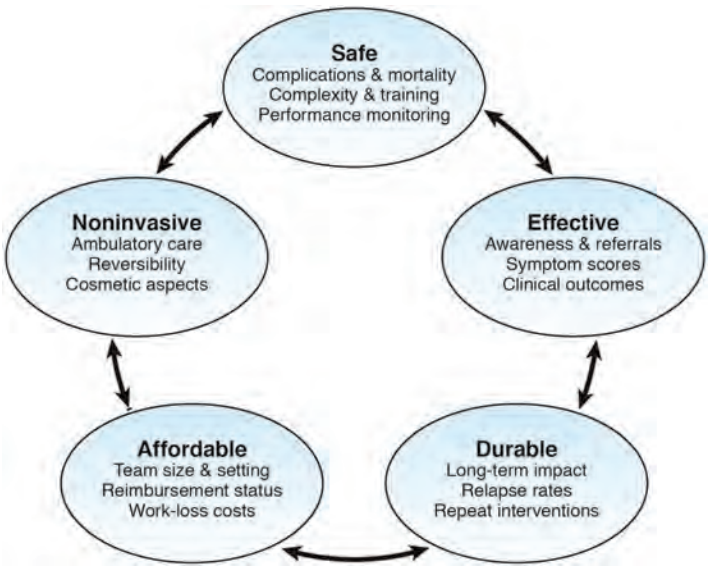

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Figure 1.The anatomy of innovations in gastrointestinal endoscopy. Major attributes that may make or break the success of technological innovations in gastrointestinal endoscopy are shown. Noninvasiveness is a key advantage of endoscopic approaches over surgical interventions closely linked to more affordability by requiring small teams, short procedure time, and quick recovery. However, novel endoscopic methods following a disruptive path of innovation and poised to compete with surgery for market share may fall short on providing effective and durable solutions. Safety has a pivot control on this process by balancing the benefits and risks of established and experimental procedures.

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