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Courtesy Daniel E. Freedberg

"When PPIs are appropriately prescribed, their benefits are likely to outweigh their risks [but] when PPIs are inappropriately prescribed, modest risks become important because there is no potential benefit," wrote Dr. Daniel E. Freedberg and coauthors of the updated guidance.

AGA CLINICAL PRACTICE UPDATE

PPIs should be prescribed sparingly

BY DEEPAK CHITNIS
Frontline Medical News

The updated best practice statements regarding the use of proton pump inhibitors detail what types of patients should be using short- and long-term PPIs.

"When PPIs are appropriately prescribed, their benefits are likely to outweigh their risks [but] when PPIs are inappropriately prescribed, modest risks become important because there is no potential benefit," wrote the authors of the updated guidance, published in the March issue of Gastroenterology (doi: 10.1053/j.gastro.2017.01.031).

"There is currently insufficient evidence to recommend specific strategies for mitigating PPI adverse effects," noted Daniel E. Freedberg, MD, of Columbia University, New York, and his colleagues.

PPIs should be used on a short-term basis for individuals with gastroesophageal reflux disease (GERD) or conditions such as erosive esophagitis. These patients can also use PPIs for maintenance and occasional symptom management, but those with uncomplicated GERD

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FDA outlines approval process for interchangeable biosimilars

BY MICHELE G. SULLIVAN
Frontline Medical News

The Food and Drug Administration has proposed a regulatory path for biosimilar biologics that are interchangeable with the reference product, paving the way for a new generation of less-expensive versions of these unique treatments.

But bringing an interchangeable biosimilar to market won't be easy. The bar for interchangeability will be high, requiring that manufacturers prove switching between the new and older products is safe. And clinicians, while cautiously optimistic, aren't thrilled with the industry payoff that could come with the designation: freedom for insurance companies and pharmacies to switch products at the dispensing level without requiring a new prescription.

The draft FDA guidance for industry, "Considerations in Demonstrating Interchangeability With a Reference Product," arises from the Biologics Price Competition and Innovation Act of 2009.

That section of the Affordable Care Act provides for abbreviated approval pathways for biological products that are demonstrated to be "highly similar" (biosimilar) to or "interchangeable" with an

See **Biosimilar** · *page 20*

INSIDE

Adjuvant chemotherapy overused in young patients with colon cancer

BY BIANCA NOGRADY
Frontline Medical News

Adjuvant chemotherapy may be overused among younger patients with colon cancer, without clear evidence of survival benefit over surgery alone, according to a report in JAMA Surgery.

Using data from 3,143 patients with histologically confirmed primary colon adenocarcinoma in the U.S. Department of Defense's Central Cancer Registry and Military Heath System medical claims databases, researchers compared overall survival in those who underwent surgery and adjuvant chemotherapy to

See **Chemo** · *page 5*

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LETTER FROM THE EDITOR: The scientific method still applies


DR. ALLEN

In this month's issue of *GI & Hepatology News*, you will find coverage of some interesting and controversial topics. There are new AGA clinical practice updates. Several years ago, the AGA Governing Board perceived a need for rapid updates targeted to practicing clinicians and focused on narrow clinical topics. These were to supplement the more in-depth and rigorously developed AGA guidelines – created using the "GRADE" methodology (*see* Gastroenterology. 2013 Dec;145:1179-81). This month we cover three new updates.

You will read about biosimilars, a new group of medications that act like branded biologic medications (we hope) but may be less expensive. These have yet to be tested in long-term clinical care.

Our flashback to 2009 concerns the first of now several articles warning us that PPIs may have rare but serious side effects.

On the political front, we are experiencing consequences to medicine and science of an administration that seeks to shake up the status quo. Gastroenterologists and other physicians differ when it comes to political ideology, but we all agree that the scientific method must be used to derive facts. While everyone is entitled to their own opinion, no one is entitled to derive factual data in the absence of empirical study.

Competing policies about health care delivery will likely yield different outcomes (number of covered lives, access to care, etc.) and we must be ready to provide solid evidence about the consequences of political decisions. Spreading risk for insurance premiums widely (something inherent in the ACA) or narrowly (as with state high-risk pools) will have real consequences for our patients and each has positive and negative attributes. We should be ready to analyze the consequences of each approach, derived from studies coming from our clinical experiences, and then advocate for best practices.

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

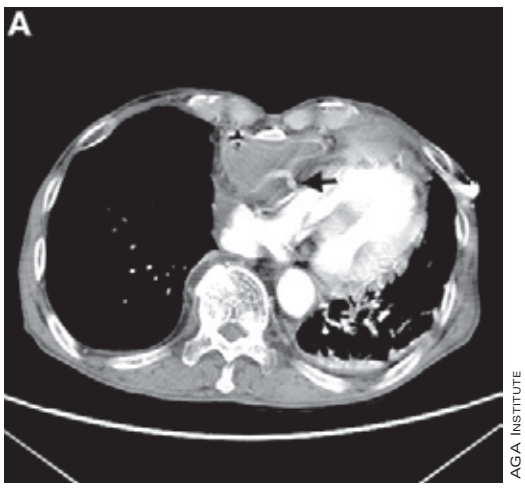
Clinical Challenges and Images

What's your diagnosis?

By Chih-Ming Lin, PhD, Yang-Yuan Chen, MD, and Hsin-Yuan Fang, MD. Published previously in Gastroenterology (2013;144:33,251-2).

A 72-year-old man was admitted to our hospital presenting with hematemesis and tarry stool for 1 day. Approximately 1 year before this admission, he received a diagnosis of T3N0M0 lower esophageal squamous cell carcinoma and underwent subtotal esophagectomy and reconstruction with gastric conduit interposition by the retrosternal root. In addition, 1 month before his admission, he received a diagnosis of constrictive pericarditis and underwent pericardiectomy. During this period of hospitalization, the patient developed persistent hematemesis followed by hypovolemic shock. Emergent esophagogastroduodenoscopy failed to identify the bleeder because numerous blood clots were present in the gastric tube. A contrast-enhanced chest computed tomography revealed a bleeder over the posterior wall of the reconstructed gastric conduit (Figure A, black arrow).

The diagnosis appears on page 18.



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References: 1. IMS Health, NPA Weekly, July 2016. **2.** Rex DK, Di Palma 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.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc*. 2015;81(1):31-53. **4.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2012.

16-00927T August 2016

Five ways HHS Secretary Tom Price may change policy

BY JULIE ROVNER
Kaiser Health News

After a bruising confirmation process, the Senate confirmed Rep. Tom Price, R-Ga., to head up the Department of Health and Human Services, by a 52-47 vote.

As secretary, Price will have significant authority to rewrite the rules for the Affordable Care Act, some of which are reportedly nearly ready to be issued.

But there is much more now within Price's purview, as head of an agency with a budget of more than $1 trillion for the current fiscal year. He can interpret laws in different ways than his predecessors and rewrite regulations and guidance, which is how many important policies are actually carried out.


SEC. PRICE

"Virtually everything people do every day is impacted by the way the Department of Health and Human Services is run," said Matt Myers, president of the Campaign for Tobacco-Free Kids. HHS responsibilities include food and drug safety, biomedical research, disease prevention and control, as well as oversight over everything from medical laboratories to nursing homes.

Price, a Georgia physician who opposes the Affordable Care Act, abortion, and funding for Planned Parenthood, among other things, could have a rapid impact without even a presidential order or an act of Congress.

Some advocates are excited by that possibility. "With Dr. Price taking the helm of American health policy, doctors and patients alike have sound reasons to hope for a welcome and long-overdue change," Robert Moffit, a senior fellow at the conservative Heritage Foundation, said in a statement when Price's nomination was announced.

Others are less enthusiastic. Asked about what policies Price might enact, Topher Spiro of the liberal Center for American Progress said at that time: "I don't know if I want to brainstorm bad ideas for him to do."

Here are five actions the new HHS secretary might take, according to advocates on both sides, that would disrupt health policies currently in force:

Birth control coverage: Under the ACA, most insurance plans must provide women with any form of contraception approved by the Food and Drug Administration at no additional cost. This has been particularly controversial in regards to religious employers who object to artificial contraception, leading to alterations in the rules and resulting in two separate Supreme Court rulings, one about

Continued on following page

Continued from previous page

private firms' rights to make religious objections and one about nonprofit religious hospitals and schools.

As secretary, Price would have two main options. He could expand the "accommodation" that already exempts some houses of worship from the requirement to any employer with a religious objection. Or, because the specific inclusion of birth control came via a regulation rather than the law itself, he could simply eliminate no-copay birth control coverage from the benefits insurance plans must offer. (This assumes continuing existence of the health law, at least for the short term.)

Medicare payment changes: The health law created an agency within Medicare, called the Center for Medicare and Medicaid Innovation, that was tasked with exploring new ways to pay doctors and hospitals that would reduce costs while maintaining quality. The HHS secretary has the authority to require doctors and hospitals to participate in the experiments and new payment models. Some have proved unpopular with physician and hospital groups, in particular the idea of paying providers so-called bundled payments for packages of care, rather than allowing them to bill item-by-item; one such package covers hip and knee replacements from the time of surgery through postsurgical rehabilitation. Price, as a former orthopedic surgeon himself, would likely act to scale back, delay, or cancel that project, since he "has been a critic in the past," said Dan Mendelson, CEO of Avalere Health, a Washington-based consulting firm.

Planned Parenthood funding: Republicans have been agitating to separate Planned Parenthood from its federal funding literally for decades. Congress would have to change Medicaid law to permanently defund the women's health group, which also performs abortions (with nonfederal funds) at many of its sites. But an HHS secretary has many tools at his disposal to make life miserable for the organization.

For example, during the Reagan and George H.W. Bush administrations, rules were put in place, and eventually upheld by the Supreme Court, that would have banned staff in federally funded family planning clinics from counseling or referring for abortion women with unintended pregnancies. The subsequent Clinton administration repealed the rules, but they could make a comeback under the new secretary's leadership.

Price could also throw the weight of the department into a probe into Planned Parenthood's ties to firms allegedly selling fetal tissue for profit, which has also been investigated by a House committee.

Tobacco regulation: After years of discord, Congress finally agreed to give the Food and Drug Administration (limited) authority to regulate tobacco products in 2009. "The core authority is statutory," said Matt Myers of the Campaign for Tobacco-Free Kids, who advocated for the law. That means Congress would have to act to eliminate many of its changes. But a secretary who opposes the law (Price voted against it at the time) could weaken enforcement, said Mr. Myers. Or he could rewrite and water down some rules, including recent ones affecting cigars and e-cigarettes.

"The secretary has very broad discretionary authority not to vigorously enforce or implement the statute in an aggressive manner," Mr. Myers said.

Conscience protections: At the very end of the George W. Bush administration, HHS issued rules intended to clarify that health care professionals did not have to participate in performing abortions, sterilizations, or other procedures that violated a "religious belief or moral conviction."

Opponents of the rules complained, however, that they were so vague and sweeping that they could apply not just to opponents of abortion, but also to those who don't want to provide birth control to unmarried women, or HIV treatment to homosexuals.

The Obama administration revised the rules dramatically, much to the continuing consternation of conservatives. They were among the few health-related items included in the health section of Trump's website before he was inaugurated and the page was taken down. "The Administration will act to protect individual conscience in health care," it said. Many expect the rules to be reinstated in their original form.

Kaiser Health News is a national health policy news service that is part of the nonpartisan Henry J. Kaiser Family Foundation.

Survival as good with surgery alone

Chemo *from page 1*

those who underwent surgery alone.

They found patients aged 18-49 years were up to eight times more likely to receive postoperative systemic chemotherapy across all tumor stages, compared with patients aged 65-75 years. The odds ratios ranged from 7.98 for stage I tumors to 2.30 for stage III tumors (JAMA Surgery. 2017 Jan 25. doi: 10.1001/jamasurg.2016.5050).

"Furthermore, young and middle-aged adults were 2.5 times more likely to receive multiagent chemotherapy regimens and most patients with information on chemotherapy regimens underwent multiagent regimens, suggesting a tendency toward more intense treatments," wrote Janna Manjelievskaia, MPH, of Walter Reed National Military Medical Center, and coauthors.

However, they found that there was no significant difference in survival between those who had surgery and chemotherapy, compared with those who had surgery alone, across age groups and tumor stage.

They did note greater overall survival among middle-aged patients with stage I and stage IV disease who were treated with surgery alone, compared with their older counterparts. Younger patients with stage III disease who received surgery alone also had slightly better survival than did older patients.

"The study suggests that more use of chemotherapy in younger patients did not result in additional survival benefits," the authors wrote.

While national guidelines advise that selected patients with stage II disease – those with inadequately sampled nodes, T3 lesions or poorly differentiated histology – can be considered for adjuvant chemotherapy, the authors argued there is no solid evidence for the effectiveness of chemotherapy in these patients.

"Patients with cancer who receive chemotherapy are vulnerable to its toxicity and adverse effects and may have reduced quality of life," they wrote. "As a result, patients may undergo decreased physical, functional, emotional, and social well-being, although these changes might be mitigated over time."

Given the additional economic and financial cost of adjuvant chemotherapy, the authors called for further research to evaluate the appropriate use of chemotherapy in colon cancer.

The John P. Murtha Cancer Center, Walter Reed National Military Medical Center, and the National Cancer Institute supported the study. No conflicts of interest were declared.

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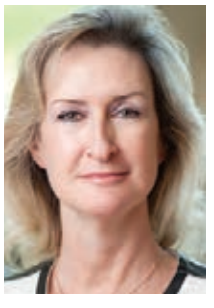
PERSPECTIVE

Improved oversight of chemotherapy needed for colon cancer



The study by Manjelievskaia et al. is a call for action, and invites contemplation and in-depth study. Appropriate treatment is vital for a patient's survival, but excess treatment may increase complications and is poor stewardship of health care funds.

Further investigation of the discrepancies in stage II would be worthwhile, and additional research on the age discrepancies in stage I disease would not only be interesting but also mandatory. Colorectal cancer tumor boards frequently concentrate on the complex care of rectal cancer and metastatic colon cancer. This is also a clear call for improved oversight of chemotherapy for colon cancer.

Tonia M. Young-Fadok, MD, is at the Mayo Clinic, Phoenix. These comments are excerpts from an accompanying editorial (JAMA Surg. 2017, Jan 25. doi: 10.1001/jamasurg.2016.5051). No conflicts of interest were declared.

FLASHBACK TO JANUARY 2009

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

The January 2009 issue of GI & Hepatology News (GIHN) featured an article on the potential drug interaction between proton pump inhibitors (PPIs) and clopidogrel.

In the study of interest, researchers retrospectively reviewed 16,000 patients prescribed clopidogrel after percutaneous coronary intervention (PCI) and found that those patients who were also on a PPI were 1.5 times as likely to suffer from a myocardial infarction, stroke, or be hospitalized for angina as those not on a PPI.

A second study mentioned in the GIHN article, a post hoc analysis of the CREDO trial, found a higher rate of ischemic events in patients on a PPI, but this increase was seen whether the patient was on clopidogrel or not. The conflicting data presented a management challenge for cardiologists and gastroenterologists alike.

It is important to note that the chair of the session where these two analyses were presented and subsequent statements from professional societies all suggested that there was no need to change practice ... but practice did change. In my own center at the time, a new potential interaction alert was found in the medical record. Some of my patients shunned their PPIs. The findings were of sufficient concern that the Food and Drug Administration added a warning on the labeling of clopidogrel regarding the concomitant use of clopidogrel and omeprazole. One study (PLoS One. 11[1]:e0145504) found a 40% drop in combined clopidogrel-PPI users after this FDA communication.

Multiple subsequent studies, including a large randomized trial, COGENT (N Engl J Med. 2010;363:1909-17), comparing omeprazole with placebo in patients on clopidogrel, found no significant interaction. A consensus document published in December 2010 acknowledged the potential risks from pharmacodynamic studies but suggested that the clinical data were unclear.

This story speaks to the power of research to change practice, the importance of effectively communicating research findings to the public, and the fact that the practice of medicine is often an exercise in balancing conflicting data on behalf of our patients.

Ziad Gellad, MD, MPH, AGAF, is associate professor of medicine in the division of gastroenterology, Duke University Medical Center, Durham, N.C.; a faculty member at the Duke Clinical Research Institute; and an Associate Editor of GI & Hepatology News.

FROM THE AGA JOURNALS

Endoscopic resection alone sufficed in many T1 CRCs

BY AMY KARON
Frontline Medical News

Patients with T1 colorectal cancer might not benefit from additional surgery after endoscopic resection unless they have positive or indeterminate resection margins or high-risk histology, according to a retrospective, population-based study of 1,315 patients.

After a median follow-up of 6.6 years, the rates of colorectal cancer (CRC) recurrence were 6.2% in patients who underwent endoscopic resection only and 6.4% in patients who also had additional surgery (P = .9), reported Tim D.G. Belderbos, MD, of University Medical Center Utrecht (the Netherlands). Rates of local recurrence also were similar between these groups (4.1% and 3.7%, P = .3), he and his associates reported in the March issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.08.041).

Among high-risk patients, however, the rates of overall recurrence were 14% with endoscopic resection only and 7% with endoscopic resection plus additional surgery (P = .06), and the rates of local recurrence were 12% and 1%, respectively (P = .004). "Based on our study, we recommend performing additional surgery after initial endoscopic resection in cases of high-risk T1 CRC, determined by high-risk histology and/or positive resection margins," the researchers concluded.

Invasive CRCs confined to the colonic submucosa (T1 CRC) present a treatment dilemma – they are usually cured by complete endoscopic resection, but up to 13% involve lymph node metastases and need additional surgery, the investigators noted. To identify predictors of recurrence and metastasis, they studied all patients diagnosed with T1 CRC in the Southeast Netherlands from 1995 through 2011. A total of 370 patients (28%) underwent endoscopic resection only, 220 (17%) underwent endoscopic resection with additional surgery, and 725 (55%) had an initial surgical resection.

Surgery after endoscopic resection was more likely when patients had positive or doubtful resection margins (P less than .001), and this link remained significant after high-risk histology, tumor location, time period, age, sex, and comorbidities were controlled for.

Endoscopic resection plus surgery did not reduce the risk of recurrence, compared with endoscopic resection only (P = .3), after the investigators accounted for age, sex, year of procedure, tumor location, and margin characteristics. Initial surgery was associated with significantly lower rates of overall and local recurrence, compared with endoscopic resection only, but the differences also lost significance in the multivariable analysis (P = .2).

Only the presence of positive resection margins significantly predicted recurrence among patients undergoing endoscopic resection (hazard ratio, 6.9; 95% confidence interval, 2.3-20.9). Positive or doubtful resection margins also predicted recurrence after initial surgery, with hazard ratios of 13.2 and 3.4, respectively.

High-risk histology – that is, poor differentiation, deep submucosal invasion, or lymphangioinvasion – was significantly associated with lymph node metastasis (OR, 2.2; 95% CI, 1.3-3.7; P less than .002), but not with recurrence after resection margins were accounted for. This might result from missing histology data or the fact that patients with high-risk histology tended to undergo surgical rather than endoscopic resection, the researchers said.

They noted several other study limitations, including a lack of details about lesions and procedures. Also, endoscopic submucosal resection was not practiced in the Netherlands during the study period, they said.

The investigators did not report funding sources and had no disclosures.

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Sofosbuvir with velpatasvir beat other HCV GT3 regimens

BY AMY KARON
Frontline Medical News

Regimens containing sofosbuvir and velpatasvir were most effective for treating both cirrhotic and noncirrhotic genotype 3 hepatitis C virus infection (HCV GT3), according to a meta-analysis reported in the March issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.10.03).

"Our analyses indicated that ribavirin significantly increases SVR [sustained viral response] rates and should be considered, if tolerated," added Floor A.C. Berden, MD, of Radboud University Medical Center, Nijmegen, the Netherlands, and her associates.

Direct-acting antiviral regimens successfully treat chronic HCV infection, but tend to perform suboptimally in HCV GT3, especially when patients are treatment experienced and have cirrhosis. Options for HCV GT3 infection include sofosbuvir combined with ribavirin, daclatasvir, or velpatasvir. But head-to-head trials of these regimens are lacking, and are unlikely to occur, in part because the Food and Drug Administration permits single-arm trials with historical controls as the comparator, the investigators said.

Adding ribavirin to a direct-acting antiviral regimen improved the odds of SVR about 2.6-fold among noncirrhotic patients and about 4.5-fold in cirrhotic patients.

Therefore, they searched PubMed, Embase, and the Web of Science database through March 15, 2016, for randomized trials and real-world studies of at least one direct-acting antiviral agent in adults with chronic HCV GT3 infection. They also manually searched abstracts presented at the 2015 conferences of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. This work yielded 27 studies: 16 randomized controlled trials, 6 single-arm studies, and 5 observational cohort studies. The researchers used a Bayesian analysis based on Markov chain Monte Carlo methods.

For patients without cirrhosis, sofosbuvir and velpatasvir with ribavirin yielded the highest estimated likelihood of SVR (99%; 95% confidence interval, 98%-100%), followed by sofosbuvir and velpatasvir without ribavirin (97%; 95% CI, 95%-99%), sofosbuvir and daclat-

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Multiomic profile in autistic children with FGIDs

BY AMY KARON
Frontline Medical News

The gut microbiomes of children with autism spectrum disorder (ASD) and functional gastrointestinal disorders (FGID) had significantly higher levels of several *Clostridium* species and lower concentrations of other bacteria, compared with neurotypical children with and without FGIDs, which correlated with increases in inflammatory cytokines, decreased tryptophan, and increased serotonin, according to a small, single-center, cross-sectional study.

This "unique multiomic profile [was] specific to ASD-FGID and ASD-FGID with abdominal pain," wrote Ruth Ann Luna, PhD, of Texas Children's Microbiome Center at Texas Children's Hospital, Houston, and her associates. The report was published online in the March issue of Cellular and Molecular Gastroenterology and Hepatology (doi: 10.1016/j.jcmgh.2016.11.008).

Children with ASD are at increased risk for FGIDs such as functional constipation, nonretentive fecal incontinence, functional abdominal pain, abdominal migraines, and irritable bowel syndrome, compared with their neurotypical peers. Changes in the gut microbiome can affect immunologic pathways and the balance between tryptophan and serotonin. This altered "microbial-gut-brain axis" has been reported in both ASD and FGID, suggesting "that altered gut-brain communications not only may play a role in the increased occurrence of FGIDs in ASD individuals, but could advance our understanding of potential risk factors for FGID in the ASD community," the researchers wrote.

'Altered gut-brain communications not only may play a role in the increased occurrence of FGIDs in ASD individuals, but could advance our understanding of potential risk factors for FGID in the ASD community.'

Previous studies of stool specimens have found higher levels of several species of *Clostridium* in pediatric ASD, compared with neurotypical children. To confirm and expand on that work, the investigators examined microbial and neuroimmune markers in rectal biopsies and blood specimens from 14 children with ASD-FGID, 15 neurotypical children with FGID, and 6 asymptomatic neurotypical children. Participants were recruited from Nationwide Children's Hospital in Columbus, Ohio. The researchers quantified microbial 16S ribosomal DNA community signatures, cytokines, chemokines, and serotonergic metabolites, and correlated results with parental responses to the Questionnaire on Pediatric Gastrointestinal Symptoms–Rome III version.

The ASD-FGID group had significantly higher numbers for ribosomal DNA sequences for *Clostridium lituseburense* (P = .002), *Lachnoclostridium bolteae* (P = .02), *Lachnoclostridium hathewayi* (P = .03), *Clostridium aldenense* (P = .04), and *Oscillospira plautii* (P = .04), compared with neurotypical children with and without FGID. Children with ASD-FGID also had significantly lower levels of *Dorea formicigenerans* (P = .006), *Blautia luti* (P = .02), and *Sutterella* species (P = .03). "Overall, our identification of clostridial species aligns with previous autism studies that have identified microbiome alterations," the researchers noted.

They also looked specifically at abdominal pain. Children with ASD-FGID and abdominal pain had significantly higher gut mucosal levels of *Turicibacter sanguinis* (P = .03), *Clostridium aldenense* (P = .004), *Clostridium lituseburense* (P = .003), *Oscillospira plautii* (P = .01), *Clostridium disporicum* (P = .049), and *Clostridium tertium* (P = .045) than did any other subgroup, the investigators found. Patients

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asvir with ribavirin (96%; 95% CI, 92%-98%), and sofosbuvir and peginterferon with ribavirin (95%; 95% CI, 91%-98%), all for 12 weeks, the investigators reported.

For patients with cirrhosis, the most effective regimen was sofosbuvir with velpatasvir for 24 weeks (estimated SVR, 96%; 95% CI, 92%-99%), followed by sofosbuvir and daclatasvir with ribavirin for 24 weeks (94%; 95% CI, 87%-98%), and sofosbuvir and velpatasvir and ribavirin for 12 weeks (94%; 95% CI, 86%-98%). The estimated efficacy of sofosbuvir and velpatasvir held up in sensitivity analyses that honed in on studies with a low risk of bias, approved regimens, or those under regulatory evaluation, patients without decompensated cirrhosis, and patients without HIV coinfection.

Adding ribavirin to a direct-acting antiviral regimen improved the odds of SVR about 2.6-fold (95% CI, 1.3-4.7) among noncirrhotic patients and about 4.5-fold in cirrhotic patients (95% CI, 2.5-7.7), the investigators reported. "In clinical practice, choice of treatment may depend on several factors, such as availability and price of direct-acting antivirals, tolerance of ribavirin, risk of adverse events or drug-drug interactions, and the presence of resistance-associated substitutions," they added. Nonetheless, these findings can help prioritize therapies for HCV GT3 infection in both clinical guidelines and practice, they emphasized.

Dr. Berden and four coinvestigators had no relevant financial disclosures. Senior author Joost Drenth, MD, PhD, disclosed serving on advisory boards and receiving research grants from several pharmaceutical companies.

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The rapid development of direct-acting antiviral agents (DAAs) to treat hepatitis C has yielded many surprises and left some gaps in our knowledge. One of the surprises was that genotype 3, previously considered "easier to treat," proved quite resistant to the first generation of DAAs.

DR. SUSSMAN

One of the gaps in knowledge was a lack of randomized and head-to-head trials for current medications. One could argue that randomized trials have limited utility in a disease with essentially no spontaneous cures, and that head-to-head trials are pointless in a rapidly evolving field where regimens may be obsolete by the time the study is completed.

On the bright side, a hard endpoint like sustained virologic response (SVR) makes comparison between trials possible.

The paper by Bergen et al. offers some guidance in closing the knowledge gap. Their meta-analysis using Bayesian Markov chain Monte Carlo methods examined the effectiveness of currently available antiviral agents in 27 studies that focused entirely on genotype 3.

All studies used antiviral agents that are currently available in the United States, and effectiveness was tested in both noncirrhotic and cirrhotic patients.

The results were uniformly excellent – 94%-99% SVR, substantially higher than reported in clinical trials. The analysis also showed that sofosbuvir plus velpatasvir was superior to sofosbuvir plus daclatasvir or sofosbuvir plus interferon plus ribavirin.

This result conforms to in vitro data that show good inhibitory activity of velpatasvir against the NS5A replication complex inhibitor in genotype 3 replicons.

The study also showed that the addition of ribavirin improved SVR in all groups, all durations of treatment, and with all drug combinations – not bad for a weak antiviral agent with an unknown mode of action.

The evolution of antiviral therapy has been amazing. After decades of incremental gains, we entered an era of dizzying progress. Genotype 3 went from great news to bad news, and genotype 1 went from a scourge to a piece of cake.

Norman L. Sussman, MD, is associate professor of surgery, and director, Project ECHO at Baylor Univerity, Houston. He has received speaking and consulting fees for AbbVie, BMS, Gilead, and Merck.

FROM THE AGA JOURNALS

BOS beat placebo for eosinophilic esophagitis

BY AMY KARON
Frontline Medical News

Budesonide oral suspension (BOS) was safe and significantly outperformed placebo on validated measures of eosinophilic esophagitis, according to a first-in-kind, multicenter, randomized, double-blind, phase II trial presented in the March issue of Gastroenterology (doi: 10.1053/j.gastro.2016.11.021).

The novel topical corticosteroid formulation yielded a significant histologic response and was associated with 3 fewer days of dysphagia over 2 weeks, compared with placebo, reported Evan S. Dellon, MD, MPH, of the University of North Carolina, Chapel Hill, and his associates. "There were no unexpected safety signals, and compliance with medication was high, suggesting that this formulation can be reliably used," they wrote. Their findings earned BOS (SHP621) an FDA Breakthrough Therapy Designation in June 2016.

Although corticosteroids are first-line therapy for eosinophilic esophagitis, symptom response in other studies has been mixed, and the Food and Drug Administration had approved neither fluticasone nor budesonide for this disease, the researchers noted. They formulated BOS to adhere better to the esophageal mucosa to enhance esophageal delivery while decreasing unwanted pulmonary deposition.

Endoscopic severity scores dropped by 3.8 points with BOS and rose by 0.4 points with placebo (*P* less than .0001). Rates of histologic response were 39% and 3%, respectively (*P* less than .0001).

For the study, they randomly assigned 93 patients aged 11-40 years with eosinophilic esophagitis to receive either placebo or 2 mg BOS twice daily. By week 12, Dysphagia Symptom Questionnaire scores had fallen by 14.3 points with BOS and by 7.5 points with placebo (*P* = .001). Endoscopic severity scores dropped by 3.8 points with BOS and rose by 0.4 points with placebo (*P* less than .0001). Rates of histologic response were 39% and 3%, respectively (*P* less than .0001). Nonresponders averaged 10 kg more body weight than responders, and had been diagnosed about 21 months earlier (average disease duration, 46 months and 25 months, respectively).

Rates of reported adverse effects were similar with BOS (47%) and placebo (50%). Individual rates of nasopharyngitis, upper respiratory infections, and oropharyngeal pain also were comparable between groups, but one patient stopped BOS after developing dyspnea, nausea, and vomiting that were considered treatment related. Esophageal candidiasis developed in two BOS recipients – a rate similar rate to that in a prior study of BOS (Clin Gastroenterol Hepatol. 2015 Jan 13. doi: 10.1016/j.cgh.2014.05.02), and a lower percentage than in other studies of topical steroids for eosinophilic esophagitis, according to the researchers. Morning cortisol levels were similar between groups, and there were no adverse laboratory effects, they added.

Patients in this trial had severe symptoms and histology and were highly compliant with treatment. They filled out at least 70% of their symptom diary, had at least 15 eosinophils per high-power frame from at least two esophageal levels on screening endoscopy, and reported at least 4 days of dysphagia during the second half of a 4-week, blinded placebo run-in period. Researchers should consider using these strict inclusion criteria in future trials of eosinophilic esophagitis, especially because previous studies have failed to show a treatment benefit for topical steroid therapy, the investigators noted.

Meritage Pharma, which is now a part of the Shire group, makes budesonide oral suspension and sponsored the study. Dr. Dellon disclosed ties to Meritage, Receptos, Regeneron, Aptalis, Banner Life Sciences, Novartis, and Roche. All five coinvestigators disclosed ties to industry, including Meritage, Shire, Receptos, Regeneron, and Biogen Idec.

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with both ASD-FGID and abdominal pain also had significantly higher levels of *C. aldenense* (*P* = .03), *O. plautii* (*P* = .04), *Tyzzerella* species (*P* = .045), and *Parasutterella excrementihominis* (*P* = .04) than did ASD-FGID patients without abdominal pain.

Both *C. disporicum* and *C. tertium* correlated with increases in the proinflammatory cytokines IL6 and interferon-gamma. Levels of these cytokines were highest in patients with ASD-FGID, and IL6 was highest of all among children with ASD-FGID with abdominal pain. Another proinflammatory cytokine, IL17A, also correlated with *Clostridia* species that were enriched in children with ASD-FGID. Both IL6 and IL17A have been implicated in autism-like phenotypes in rodents, the researchers noted. Several other cytokines also were linked to ASD-FGID, and abdominal pain correlated significantly with increases in MCP-1 (*P* = .03) and eotaxin (*P* = .03).

Gut mucosal levels of tryptophan were significantly lower among children with ASD-FGID, compared with neurotypical children, either with (*P* = .006) or without (*P* = .009) FGID. In contrast, gut mucosal levels of 5-HIAA, the primary metabolite of serotonin, were significantly higher among children with ASD-FGID, compared with neurotypical children (*P* = .01). Increased 5-HIAA also correlated significantly with abdominal pain (*P* = .04). Six species of bacteria correlated significantly with tryptophan or serotonin, implicating the gut microbiome in the serotonin pathway.

"Although these initial findings are correlative, these data form the framework for future studies targeting tryptophan-serotonin metabolism and inflammatory pathways in FGID in ASD," the researchers concluded.

The U.S. Department of Health and Human Services funded the work. The investigators had no relevant disclosures.

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Autism-spectrum disorder is a serious and increasingly prevalent developmental behavior disorder often accompanied and aggravated by a range of gastrointestinal and cognitive dysfunctions. Its etiology probably involves maternal diet and inflammatory events that alter central nervous system neurodevelopment critical to the cognition of social interaction. Candidate causal products of these events include the cytokines IL-6 and IL-17A, and certain bioactive amines, notably serotonin. Functional gastrointestinal disorders share these same molecules as biomarkers and disease modifiers, probably elicited in part by the intestinal microbiome. Hence, the comorbidity in ASD suggests these two disease processes are etiologically related.

The study by Luna and colleagues tightens the case for a microbial hub and serotonin and cytokine spokes in the gastrointestinal dysfunction of ASD: elevated mucosal tissue levels of select microbial taxa, mainly members of the genus *Clostridium,* and mucosal production of cytokines and serotonin-pathway bioamines associated with these and other select microbial species. Important and challenging questions loom ahead. What are the direct mucosal cell types and functions targeted of this network for the microbiota, and via what microbial products? Might they elicit epithelial or mucosal hematopoietic cell cytokine production that in turn causes mucosal bioamine secretion? And, what associated microbiota and products are just secondarily altered and not causally involved? The exciting study of Luna and colleagues raises confidence for this path ahead, and its promise for clarifying ASD pathogenesis and uncovering targetable elements for intervention.

Jonathan Braun, MD, PhD, AGAF, is professor and chair of pathology and laboratory medicine, UCLA David Geffen School of Medicine, UCLA Health System, Los Angeles. He has no conflicts of interest.

FROM THE AGA JOURNALS

Sterile fecal filtrate effectively treated recurrent CDI

BY AMY KARON
Frontline Medical News

Sterile fecal filtrate transplantation (FFT) effectively treated five cases of symptomatic chronic-relapsing *Clostridium difficile* infection, investigators reported.

The procedure restored normal bowel habits and eliminated symptoms through the end of the study – that is, for at least 6 months – in all patients, Stephan J. Ott, MD, and his associates wrote (Gastroenterology. 2016. doi: 10.1053/j.gastro.2016.11.010).

Proteome analyses did not identify proteins likely to explain this efficacy, but 16S rRNA gene sequencing did demonstrate diverse bacterial DNA signatures in the filtrates, and tests of virus-like particles yielded "a complex signature of macrophages," reported Dr. Ott of University Hospital Schleswig Holstein in Kiel, Germany, and his associates.

Additional tests suggested that recipients' microbiomes continued to change weeks after FFT. "This open-label series strongly suggests that FFT should be evaluated in a controlled setting in comparison with standard fecal microbiota transplantation," the researchers concluded.

Fecal microbiota transplantation (FMT) effectively treats recurrent *Clostridium difficile* infection (CDI), but even "the most rigorous and costly donor screening procedures, or defined panels of bacteria, cannot exclude the risk of transferring unknown pathogens or undetectable functional characteristics within the living microorganisms to the recipient, including bacterial or viral risk factors for metabolic diseases, cancer, atopy, or autoimmunity," the investigators wrote.

Therefore, they performed sterile FFT in five patients who were positive on at least two of three tests: enzyme-linked immunosorbent assay for *C. difficile*–specific glutamate dehydrogenase; *C. difficile* toxin enzyme-linked immunosorbent assay; and culture of toxin-producing *C. difficile*. Patients chose their own stool donors, who were then screened based on published guidelines (Clin Gastroenterol Hepatol. 2011;9[12]:1044-49). Next, "slurries" were prepared from donor stool and filtered with a custom-built air pressure filtration system, yielding a "light brown, clear liquid with a subjectively less unpleasant and intensive odor" than conventional FMT stool preparations. Bacterial cultures of these filtrates yielded no growth, whereas donor stool cultures showed profuse growth of aerobic and anaerobic bacterial colonies, Dr. Ott and his associates said.

Patients became symptom-free

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2-4 days after undergoing FFT. Notably, one patient had previously undergone FMT, which led to acute fever and diarrhea and recurrence of baseline symptoms after 3 months. This patient did not develop fever or diarrhea after FFT, was symptom-free after 3 days, and remained symptom-free until the study ended 2 years later, the researchers said. All other patients also remained symptom-free through the end of the study, that is, for 6 months to more than 2 years.

Analyses of 16S rRNA revealed substantial longitudinal shifts after FFT that often were present by week 1 and remained stable until week 6, the investigators said. Further tests confirmed marked shifts in bacterial phylotypes and in their relative abundance over time. Repeated virus analyses of one patient also showed that the phageome shifted over time to resemble that of the donor.

Patients were between 49 and 75 years old, three were female and two were male, and all had received more than one antibiotic before their first episode of CDI. Antibiotics for CDI had included metronidazole, vancomycin, and rifaximin. Comorbidities included pseudomembranous colitis, renal failure, HIV infection, epilepsy, and chronic heart failure, and medical histories included recurrent diverticulitis with sigmoid resection, gastric carcinoma, and colon cancer.

"It is important to keep in mind that, in contrast to conventional FMT, transferring sterile FFT filtrates cannot be expected to establish a microbiota similar to that of the donor in the receiving patient," Dr. Ott and his associates noted. Instead, bacterial DNA in the filtrate might trigger the re-establishment of the recipient microbiome, they said. Bacterial cell wall fragments or bacteriophages also might play a role, they added.

The German Excellence Cluster and CONARIS Research Institute AG supported the work. Dr. Ott reported having lectured for Allergosan. Two coinvestigators reported employment with CONARIS. A third coinvestigator reported shareholder relationships with CONARIS, Allergosan, Danone, and Nestle and lectureship compensation from Allergosan. The other eight coinvestigators had no relevant conflicts of interest.

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The remarkable efficacy of fecal microbial transplant in recurrent *C. difficile* infection provides a compelling example of ecologic microbiome-based therapy. Its mechanism is widely considered to be the restoration of select microbial species that suppress *C. difficile* colonization and virulence in healthy individuals. Identification of such suppressive microbiota is still at an early stage, with empirical studies revealing effective synthetic microbial consortia, and evidence of some modes of action, such as bile salt metabolism (Nature. 2015;517:205-8; PLoS Pathog. 2012;8:e1002995).

Clouding this elegant concept is the provocative new study of Dr. Ott and his colleagues. Prompted by long-term safety concerns, they evaluated the efficacy of a donor fecal microfiltrate lacking viable intact organisms. Indeed, in five patients, long-term eradication of *C. difficile* was achieved with a single dose. This observation indicates that the initial action of fecal transplant may not require restoration of viable organisms into the antibiotic-damaged ecosystem.

What mechanisms might account for the therapeutic action of organism-free fecal microfiltrate? First, this material is laden with a complex, potentially distinct mix of microbial products and particulates (Cell. 2016;165[5]:1106-19) from donor origin or ex vivo processing. These biologicals may induce immune processes to promote control of *C. difficile* directly or via changes in other commensals of the patient's microbiome. Second, the microfiltrate retains abundant and diverse bacteria-targeting viruses of the fecal stream. Perhaps certain viruses, deficient in patients, target *C. difficile* and/or beneficially reshape microbial composition (Cell Mol Gastroenterol Hepatol. 2015;1[1]:28-40). So, *C. difficile* challenges us once more into the breach with new insights ahead for the principles and practice of ecologic microbiome therapy.

Jonathan Braun, MD, PhD, AGAF, is professor and chair of pathology and laboratory medicine at the University of California, Los Angeles. He has no conflicts of interest.

DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz

Q1: A 14-year-old boy with a history of mild seasonal allergies presents to the emergency room with chest pain and discomfort after eating a steak 2 hours ago. He is having trouble swallowing and feels there is a piece of food stuck in his chest, and he points to his mid-sternum. He tells you this has happened several other times over the past year, and he felt better after he vomited. His physical examination is entirely normal.

He is taken to the operating room for emergency endoscopy where a large piece of steak is removed from his mid-esophagus, without complication. Biopsies of the mid-esophagus demonstrate acute and chronic inflammatory changes in the lamina propria with 35 eosinophils per high-powered field.

What is the most likely diagnosis?
A. Eosinophilic esophagitis.
B. GERD.
C. Inflammatory bowel disease.
D. Fungal esophagitis.
E. Achalasia.

Q2: A 52-year-old man with history of recurrent variceal bleeding presents for evaluation. He has an HIV infection that is controlled, with undetectable virus and CD4 count of 423 cells/mcL. He has no known underlying liver disease. He is currently on etravirine, emtricitabine, and tenofovir. He has previously taken didanosine. His physical exam is unremarkable and his laboratory data reveals a normal CBC, normal INR, and normal liver enzymes. Testing for hepatitis B and C and autoimmune liver disease, as well as iron overload and other etiologies of chronic liver disease are all negative.

Ultrasound of the abdomen notes a normal-appearing liver and patent portal and hepatic veins. A liver biopsy demonstrates mildly dilated portal veins and mild fibrosis of the portal venous walls. There is no evidence of cirrhosis on the liver biopsy.

Which of the following statements is true regarding noncirrhotic portal hypertension in this patient?
A. Clinical presentation with ascites is more common than variceal bleeding.
B. A history of didanosine use is consistent with his clinical presentation.
C. Presentation with normal liver function is atypical in this setting.
D. The underlying pathology is related to progressive sinusoidal fibrosis.
E. This patient is at low risk for developing portal vein thrombosis.

Q1: Answer: A
Critique: This is a classic presentation of eosinophilic esophagitis (EoE). As many as half of older children with food impactions suffer from EoE. EoE is characterized by a severe, eosinophilic infiltration of the esophagus that may respond to acid inhibition, systemic or topical steroid therapy, or removal of dietary allergens. Epidemiologic studies suggest a rising incidence in the United States in both children and adults, with at least one case occurring in every 10,000 children each year. Treatment is aimed at alleviating symptoms and healing esophageal inflammation. Allergy testing should be performed at the time of diagnosis; however, radioallergosorbent tests and skin-prick tests are often negative, and only half of affected children have a antecedent history of other allergic symptoms.

A five-food elimination diet can be helpful for many affected children and adults, although adherence to the diet can be difficult. There is a group of affected children who respond to high doses of proton pump inhibitors, and most patients respond to either systemic or topical steroid therapy. Even with therapy, some patients go on to develop esophageal strictures and may need serial or repeated dilatations.

While eosinophilic infiltration and inflammation may be present with gastroesophageal reflux disease and associated esophagitis, the number of eosinophils seen in this boy's biopsies is much more consistent with EoE. Moreover, stricture formation as a result of peptic esophagitis in a child this age would be extremely rare. While inflammatory bowel disease may be associated with eosinophilic infiltration of the intestinal tract, isolated esophageal Crohn's disease would be extraordinarily rare. Our patient has no history of any immune deficiency or steroid use that would predispose to fungal esophagitis. Achalasia typically presents with gradually worsening symptoms, and the obstruction would be at the lower esophageal sphincter, not in the mid-esophagus.

References

1. Liacouras C., Furuta G., Hirano I., et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128:3-20.

2. Furuta G., Liacouras C., Collins M., et al. Eosinophilic esophagitis in children and adults: A systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology. 2007;133:1342-63.

Q2: Answer: B
This patient, with no imaging or laboratory findings to suggest cirrhosis, most likely has noncirrhotic portal hypertension (NCPH). There is now a well-described association between HIV and NCPH with the prevalence of NCPH in HIV estimated to be –0.5% to 1%. Patients typically are unaware of any underlying liver disease until presentation with variceal bleeding. Variceal bleeding is a much more common manifestation of NCPH than ascites. Clinical presentation with normal hepatic enzymes and normal hepatic synthetic function is a very typical feature in these patients. Although the exact etiology is not fully understood, NCPH in HIV is likely related to highly active antiretroviral therapy, particularly didanosine use, hypercoagulability, microbial translocation from the gut, and direct effects of HIV. NCPH is a presinusoidal lesion, and liver biopsy may reveal paucity of portal vasculature and focal obliteration of small portal veins. Portal vein thrombosis in patients with HIV and NCPH is common and has been observed in 25%-75% of patients.

References

1. Vispo E., Morello J., Rodriguez-Novoa S., Soriano V. Noncirrhotic portal hypertension in HIV infection. Curr Opin Infect Dis. 2011;24:12-8.

2. Khanna R., Sarin S.K. Noncirrhotic portal hypertension – Diagnosis and management. J Hepatol. 2014;60:421-41.

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Don't discount octogenarian liver transplant grafts

BY DAN WATSON
Frontline Medical News

Donors aged 80 years or older are not necessarily inferior for a liver transplantation (LT) graft, compared with young ideal donors (aged 18-39 years), according to an analysis of the perioperative LT period.

While "the potential risks and benefits associated with the use of livers from octogenarian donors must be closely weighed, with careful donor evaluation, selective donor-to-recipient matching and skilled perioperative care, octogenarian grafts do not affect the short-term course of patients undergoing LT," concluded Gianni Biancofiore, MD, of Azienda Ospedaliera-Universitaria Pisana, Pisa, Italy, and his coauthors (Dig Liver Dis. 2017. doi: 10.1016/j.dld.2017.01.149).

The authors reviewed a database of LT procedures performed at their facility from 2001 to 2014. Of the procedures, 179 patients received a graft from a donor aged 18-39 years; 167 patients received a graft from a donor aged 80 years or more.

Perioperative differences were insubstantial in terms of cardiovascular complications ($P = .2$), respiratory complications ($P = 1.0$), coagulopathy ($P = .5$), and incidence of perfusion syndrome ($P = .3$). Median ICU length of stay of the two groups was identical ($P = .4$). No differences in terms of death or retransplant were observed during the ICU stay.

The authors declared no conflicts of interest.

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AGA statement on U.S. travel ban

In early February, AGA released the following statement on the U.S. travel ban:

Science and illness ignore borders and political divides. That is why AGA is concerned that the recent U.S. executive order on immigration could limit scientific exchange, delay patient care, and impair medical training.

AGA is committed to diversity, which includes race, ethnicity, and national origin. Diversity within training programs and laboratories in the United States built today's practice of gastroenterology. Scientists from around the world publish in our journals, work in our laboratories, train in our programs, and present data at Digestive Disease Week.® This exchange leads to better patient care, and very sick patients travel to the U.S. from around the world for the best digestive health care.

In light of these concerns, AGA adds our support to a growing number of medical institutions urging the administration to consider the devastating impact of the executive order on the health of the nation that will result from turning away patients, health professionals, and researchers. The recent immigration policy is clearly detrimental to America's leadership role in advancing health care and to the standing of the U.S. within the international community.

"Know that the policies of AGA's home country in no way reflect our position as an organization, and we continue to welcome and support physicians and investigators from all nations," said AGA Institute President Timothy Wang, MD, AGAF. "We understand the impact that the recent ban has had on many, and apologize for any hurt or disruption it may have caused in your lives or careers."

To better advocate on behalf of international members and patients, Dr. Wang invites members to the AGA Community, either publicly or anonymously, to share your stories about how a travel ban could affect your patients, practice, academic center, training program, or lab.

For more updates, please visit gastro.org.

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March is Colorectal Cancer Awareness Month

Each year, AGA participates in a series of activities in support of Colorectal Cancer Awareness Month – and 2017 is no exception. March provides us with an important platform to help remind patients of the necessity of getting screened. Here are a few easy ways to join us in raising awareness:

- **In-person:** Take time this month to talk to your patients about their personal history and encourage timely screening. Visit www.gastro.org/CRC for materials you can provide to your patients to help them understand risk factors and screening options.
- **On your practice website:** When patients visit your website, make sure there is a prominent CRC screening reminder. You can link to AGA's patient materials or use our awareness videos (also available via the above link) to help spread the word.
- **On Facebook:** AGA will be running a campaign throughout March to remind patients over 50 to get screened. Make sure to like us (facebook.com/AmerGastroAssn) to see our CRC posts, which you can share with your family and friends. If your practice has a Facebook page, the page can share all of our CRC awareness materials, as well.
- **On Twitter:** Tweeting is a great way to raise awareness among the public. Follow @AmerGastroAssn (twitter.com/AmerGastroAssn) for information on Twitter chats you can take part in to help raise awareness.

With your support, we can improve the public's understanding of this deadly cancer and continue to increase screening rates.

Stay tuned to AGA eDigest and AGA's website (gastro.org) for timely CRC Awareness Month updates, and join CRC-related discussions with other AGA members on the AGA Community (community.gastro.org).

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Registration open for 2017 AGA Postgraduate Course

Step beyond basic learning and get the full scope of gastroenterological and hepatological advances at the 2017 AGA Postgraduate Course.

Registration is now open at pgcourse.gastro.org. Scheduled for May 6 and 7, 2017, in conjunction with Digestive Disease Week®, you will join your colleagues in Chicago, IL, to have world-renowned leaders test your knowledge in real time and provide your pathway for optimal care that will guide your clinical decisions all year long.

This live activity is pending eligibility for a maximum of 12 *AMA PRA Category 1 Credits*™ and maintenance of certification points.

Additional details, including the program agenda and videos from the course directors, are available online. Also, information about the 2017 resources is now available on the AGA website.

Register today and save. Compared with other gastroenterology postgraduate courses, AGA's is the most cost effective. All six general sessions plus your choice of one luncheon breakout session and one case-based breakout session are included in the price. The cost to attend is discounted when you register by March 22:

- **AGA trainee members pay only $90.**
- **AGA young GI members pay only $345.**
- **Other AGA member types pay $75 less than their nonmember colleagues.**

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MACRA is not going away: Will you be ready?

Despite potential repeal of the Affordable Care Act under the new administration, the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) and commitment to cost-effective, value-based care is here to stay.

Congress overwhelmingly passed MACRA legislation with bipartisan support in both chambers of Congress to overhaul the way that physicians are reimbursed under Medicare.

Ignore MACRA in 2017, and you will face an automatic reduction of 4% to your payments under Medicare in 2019.

MACRA will eventually transition physicians toward more value-based payments. Ignore MACRA in 2017, and you will face an automatic reduction of 4% to your payments under Medicare in 2019.

You should take advantage of 2017 being a transition year during which time you can pick your own pace for participation to help you increase your earning potential. If your practice is already reporting to the 2016 Physician Quality Reporting System (PQRS), then you will be familiar with some of the 2017 options for participation that could qualify you for a reimbursement incentive in 2019 under MACRA.

If you have not participated in PQRS in 2016 or previous years, you need to start gathering information for your practice to begin reporting through one of the new MACRA 2017 reporting options by **Oct. 2, 2017.**

Quality accounts for the highest percentage of your score and will help you to maximize your potential for a positive adjustment.

AGA can help – check out our MACRA resources at gastro.org/MACRA and on the AGA Community.

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Legacy Society members sustain research

Research has brought so much to our specialty and advanced the science and practice of gastroenterology. Research is made possible through funding. AGA Legacy Society members are showing their gratitude for what funding and research has brought to our specialty by giving back.

Legacy Society members are the most generous individual donors to the AGA Research Foundation. Members of the AGA Legacy Society provide tax-deductible gifts to the AGA Research Foundation of $5,000 or more per year for 5 years ($25,000 total) or $50,000 or more in a planned gift, such as a bequest. All Legacy Society contributions go directly to support research awards.

"I was at a crossroads in my career when I received funding from the AGA," said Michael Camilleri, MD, AGAF, AGA Past President. "Having been personally a recipient of awards from the AGA Research Foundation, I believe it is now important to give back. This is one of the ways I will impact not only the careers of young colleagues but ultimately patient care, as well."

The AGA Research Foundation's mission is to raise funds to support young researchers in gastroenterology and hepatology. More than 870 researchers have benefited from our support since 1984 – with more than 90% of AGA Research Scholar Award recipients in the past 10 years continuing on to exceptional research careers. These research grants are funded through the generosity of donors.

"To understand the fundamental mechanism of disease process, particularly chronic diseases is always a challenge, but it is critical to be able to interfere with the disease process, halt progression and hopefully achieve a cure," remarked Kiron M. Das, MD, PhD, AGAF. "Research has to be continued, and we have to train young investigators. On behalf of my wife and myself, we want to thank the AGA Research Foundation for its commitment to promote discovery. It is critical that we support and give to the AGA Research Foundation."

Donors who make gifts at the Legacy Society level before DDW® will receive an invitation to the annual Benefactors' Dinner at The University Club of Chicago. Individuals interested in learning more about Legacy Society membership may contact Stacey Hinton Tuneski, Senior Director of Development at stuneski@gastro.org or via phone (301) 222-4005. More information on the AGA Legacy Society including the current roster and acceptance form is on the foundation's website at www.gastro.org/legacysociety.

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A celebration of research support

Beginning with a memorable gathering at the United States Library of Congress in 2007, the AGA Benefactors' Dinner has welcomed members of the AGA Legacy Society and other AGA dignitaries to special locations nationwide. The University Club of Chicago will be the location of the 2017 AGA Research Foundation Benefactors Dinner during DDW in Chicago. Guests will enjoy a wonderful evening in the historic setting established in 1887 to foster an appreciation for literature and the arts. Members of the AGA Legacy Society will be among the distinguished honorees at the annual event.

Courtesy The University Club of Chicago

The University Club of Chicago

AGA CLINICAL PRACTICE UPDATE

Proceed with care

PPI CPU *from page 1*

should be weaned off PPIs if they respond favorably to them.

If a patient can't be weaned off PPIs, then ambulatory esophageal pH and impedance monitoring should be done, in order to determine if the patient has a functional syndrome or GERD. Lifelong PPI treatment should not be considered until this step is taken, according to the new best practice statements.

"Short-term PPIs are highly effective for uncomplicated GERD [but] because patients who cannot reduce PPIs face lifelong therapy, we would consider testing for an acid-related disorder in this situation," the authors explained. "However, there is no high-quality evidence on which to base this recommendation."

Patients who have symptomatic GERD or Barrett's esophagus, either symptomatic or asymptomatic, should be on long-term PPI treatment. Patients who are at a higher risk for NSAID-induced ulcer bleeding should take PPIs if they continue to take NSAIDs.

When recommending long-term PPI treatment for a patient, the patient need not use probiotics on a regular basis; there appears to be no need to routinely check the patient's bone mineral density, serum creatinine, magnesium, or vitamin B_{12} level on a regular basis. In addition, they need not consume more than the Recommended Dietary Allowance of calcium, magnesium, or vitamin B_{12}.

Finally, the authors state that no evidence has been found indicating that PPI formulations can be ranked in any way based on risk.

These recommendations come from the AGA's Clinical Practice Updates Committee, which pored through studies published through July 2016 in the PubMed, EMbase, and Cochrane library databases. Expert opinions and quality assessments on each study contributed to forming these best practice statements.

"In sum, the best current strategies for mitigating the potential risks of long-term PPIs are to avoid prescribing them when they are not indicated and to reduce them to their minimum dose when they are indicated," Dr. Freedberg and his colleagues concluded.

The researchers had no relevant disclosures.

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Increase in U.S. drug spending slowed in 2016

BY RICHARD FRANKI
Frontline Medical News

Prescription drug spending for those with employer-sponsored insurance increased by 3.8% in 2016, compared with a rise of 5.2% in 2015, according to pharmacy benefits manager Express Scripts.

Commercial plans managed by Express Scripts saw the cost of prescription drugs rise by 2.5% per person, while utilization was up by 1.3%. That represents a 27% drop from 2015, when drug costs rose 2.0% and use went up by 3.2%, Express Scripts said in its "2016 Drug Trend Report."

Spending on specialty drugs increased by 13.3% in 2016, which was the smallest rise since 2003. Spending on traditional drugs, which make up almost two-thirds of total spending, decreased by 1.0% in 2016, the report noted.

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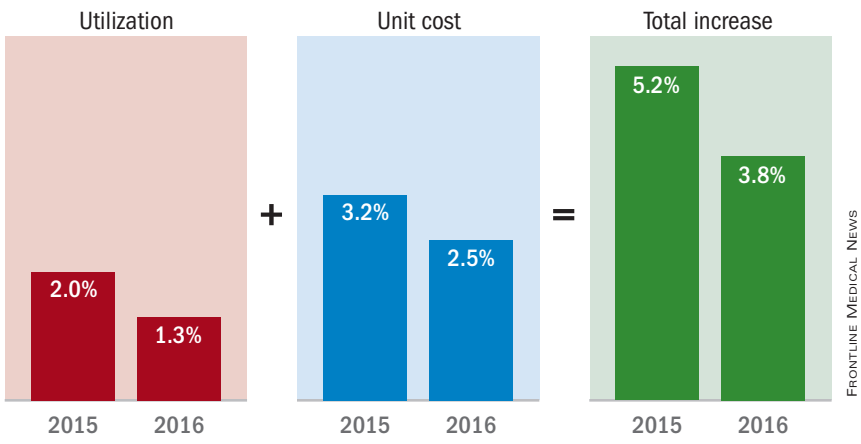
Increases in drug use and cost per person, 2015 and 2016



FRONTLINE MEDICAL NEWS

Note: Express Scripts is the pharmacy benefit manager for 85 million people and processes 1.4 billion prescriptions annually.

Source: Express Scripts "2016 Drug Trend Report"

CLINICAL CHALLENGES AND IMAGES

The diagnosis

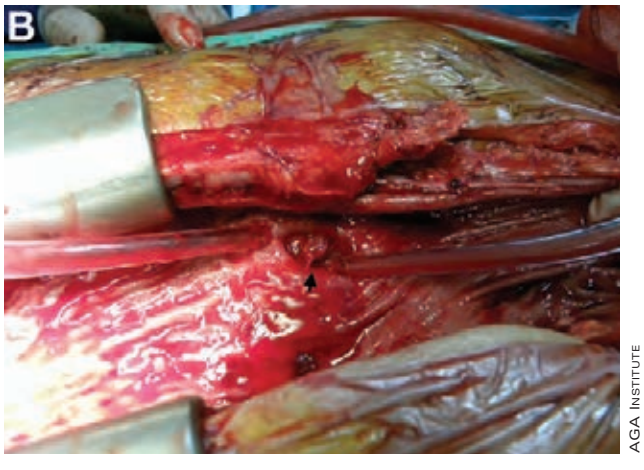
Answer to "What's your diagnosis?" on page 2: Gastrocardiac fistula with active bleeding

Active bleeding from a fistula between the right ventricle and reconstructed gastric conduit was identified after opening the gastric conduit (Figure B, black arrow). The surgeon decided to resect the gastric tube, create an esophagotomy and feeding jejunostomy, and perform a cardiorrhaphy with primary suture closure and peritoneal patch repair. The bleeding stopped after the operation, and the patient was discharged without incident 3 weeks later.

Only seven cases of fistula between postesophagectomy gastric conduits and cardiac chambers, including this case, have been reported in English literature. The disease mortality rate is as high as 60%.[1] Several predisposing risk factors exist for gastrocardiac fistula, including malignancy, radiation, ischemia, and peptic ulcer disease.[1] We surmised that the previous pericardiectomy was the predisposing factor in this case.

Fistula rarely develops between the upper gastrointestinal tract and adjacent structures, including the trachea, bronchi, pleura, aorta, pericardium, and heart.[2,3] The symptoms differ depending on the location of the fistula, and recurrent bronchopneumonia, pleuritis, mediastinitis, pericarditis, and upper gastrointestinal bleeding may be present. Because of the high mortality rate, physicians should be alert to these fatal fistula. If fistula is suspected, a contrast radiological study and direct endoscopic visualization can be employed to establish a diagnosis.

Gastrocardiac fistula is a rare cause of upper gastrointestinal bleeding. The majority of diagnoses were made at autopsy. Only aggressive and emergent operative intervention can offer patients a chance of survival because they tend to deteriorate rapidly.[1] This case of gastrocardiac fistula occurred after esophagectomy with gastric conduit reconstruction and a pericardiectomy. Immediate surgery is required for life-threatening upper gastrointestinal bleeding if gastrocardiac fistula is suspected. Patient survival is likely after immediate operation.



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References

1. Pentiak, P., Seder, C.W., Chmielewski, G.W., et al. Benign post-esophagectomy gastrocardiac fistula. Interact Cardiovasc Thorac Surg. 2011;13(4):447-9.
2. Schouten van der Velden, A.P., Ruers, T.J., Bonenkamp, J.J. A cardiogastric fistula after gastric tube interposition (A case report and review of literature). J Surg Oncol. 2007;95(1):79-82.
3. Rana, Z.A., Hosmane, V.R., Rana, N.R., et al. Gastro-right ventricular fistula: a deadly complication of a gastric pull-through. Ann Thorac Surg. 2010;90(1):297-9.

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AGA CLINICAL PRACTICE UPDATE

Using FLIP to assess upper GI tract still murky

BY DEEPAK CHITNIS
Frontline Medical News

New clinical practice advice has been issued for use of the functional lumen imaging probe (FLIP) to assess disorders of the upper gastrointestinal tract, with the main takeaway being the device's value in diagnosing achalasia.

"Although the strongest data appear to be focused on the management of achalasia, emerging evidence supports the clinical relevance of FLIP in the assessment of disease severity and as an outcome measure in [eosinophilic esophagitis (EoE)] intervention trials," wrote the authors of the update, led by John E. Pandolfino, MD, AGAF, of Northwestern University, Chicago. The report is in the March issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.10.022).

In reviewing relevant studies, Dr. Pandolfino and his coauthors found that FLIP is useful in determining esophagogastric junction (EGJ) function, mainly by allowing clinicians to more accurately evaluate the luminal opening to determine bolus flow. This could be more of a reliable diagnostic tool than simply using lower esophageal sphincter (LES) relaxation. One of the studies the authors reviewed, published in 2012 and led by Wout O. Rohof of the Academic Medical Center in Amsterdam, used an EndoFLIP to evaluate EGJ distensibility in healthy controls and patients with achalasia.


DR. PANDOLFINO

In terms of evaluating the LES, however, FLIP can be used during laparoscopic Heller myotomy or peroral endoscopic myotomy (POEM) as a way of monitoring the LES. Using FLIP this way can help clinicians and surgeons personalize the procedure to each patient, even while it's ongoing. FLIP also can be used with dilation balloons, with the balloon diameter allowing dilation measurement without the need to also use fluoroscopy.

For treating gastroesophageal reflux disease (GERD), the evidence in existing literature points with less certainty toward use of FLIP.

"The role of FLIP for physiologic evaluation and management in GERD remains appealing; however, the level of evidence is low and currently FLIP should not be used in routine GERD management," the authors explained. "Future outcome studies are needed to substantiate the utility of FLIP in GERD and to develop metrics that predict severity and treatment response after antireflux procedures."

FLIP can be used in managing EoE, but is recommended only in certain scenarios. According to the authors, FLIP can be used to measure esophageal narrowing and the overall esophageal body. FLIP also can be used to measure esophageal distensibility, and, in the case of at least one study reviewed by the authors, allows "significantly greater accuracy and precision in estimating the effects of remodeling" in some patients.

Dr. Pandolfino and his colleagues warned that "current recommendations are limited by the low level of evidence and lack of generalized availability of the analysis paradigms." They noted the need for "further outcome studies that validate the distensibility plateau threshold and further refinements in software analyses to make this methodology more generalizable."

Overall, the authors concluded, more study still needs to be done to ascertain exactly what FLIP is capable of and when it can be used to greatest effect. In addition to evaluating its benefit in patients with GERD, research should focus on how to make data obtained via FLIP easier to interpret and put to use.

"More work is needed [that] focuses on optimizing data analysis, standardizing protocols, and defining outcome metrics prior to the widespread adoption [of FLIP] into general clinical practice," the authors wrote.

Dr. Pandolfino disclosed relationships with Medtronic and Sandhill Scientific. Other coauthors had no relevant financial disclosures.

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Banking on discounts

Biosimilars *from page 1*

FDA-approved biological product.

The difference between these appellations is subtle but critical to the regulatory process – and perhaps to patient safety. Regulators recognize that the structure of these large, highly complex molecules can never precisely replicate the reference product. But to be labeled a "biosimilar," developers must prove that the new product functions essentially the same; there can be no clinically meaningful differences in terms of safety, purity, and potency. Unlike a generic medication, a biosimilar can't be substituted for its reference product at the pharmacy level. If a physician wants the patient on that biosimilar, the script must specify it.

Interchangeables jump a higher regulatory bar

An "interchangeable biosimilar," though, would have to jump a higher regulatory bar. Not only must it produce the same clinical result as the reference product, it also must be benignly interchangeable with it, conferring no additional risk if a patient switches from the reference to the biosimilar and back again. A pharmacist could, if permitted by state law, substitute an interchangeable product for the reference product without going through the prescriber.

Like biosimilars, interchangeable products need not be tested in every disease for which the reference product is approved, according to the document. Once they are proved safe for one indication, those data can be extrapolated to allow approval for the other indications as well. Nor do biosimilars need to prove efficacy per se, as their molecular similarity to the reference product ensures that they bind to the same receptor and exert the same therapeutic effect.

The biosimilar/interchangeable market has been slow to take off in the United States. There are no approved interchangeable biosimilars, and only four biosimilars – three of which were approved in 2016:

- Sandoz' filgrastim-sndz (Zarxio).
- Pfizer's and Celltrion's infliximab-dyyb (Inflectra).
- Sandoz' etanercept-szzs (Erelzi).
- Amgen's adalimumab-atto (Amjevita).

Switching studies are the key to achieving the interchangeable designation, according to the FDA document. They must include at least two full switches between the candidate product and the reference product, which must be licensed in the United States.

But because these products are so structurally diverse, the FDA isn't imposing a one-size-fits-all process on them. Instead, the molecular complexity and immunogenicity of each product will dictate its approval requirements.

Those with relatively low structural complexity, high molecular similarity to the reference product, and a low incidence of immunogenic adverse events may only need a single switching study to achieve the "interchangeability" designation.

The bar will be higher for a product with high structural complexity that is not as similar to the reference product, or which has been associated with immunogenic adverse events. For this product, FDA might also require extensive safety postmarketing data for the product as a licensed biosimilar, as well as a switching study.

'In these biologic compounds, very small differences can be amplified and alter therapeutic response.'

DR. HANAUER

Pharmacokinetics, pharmacodynamics, immunogenicity, and safety will be the primary endpoints of a switching study. Efficacy data are not necessary but can be used as supportive endpoints. Any safety signals in a switching study would raise regulatory eyebrows whether they came from the candidate product or the reference product. Since the study replicates what could happen if the two were used sequentially, it makes little difference from which product the event might arise.

"If an apparent difference in immune response or adverse events is noticed between the switching and nonswitching arms of the study ... it would raise concerns as to whether the proposed interchangeable product is interchangeable, regardless of whether the proposed interchangeable product or the reference product or the switching of the two products actually caused the event," the document notes.

The E.U. vs. U.S. experience

The United States is only now getting a taste of what has become common fare in the European Union, said Angus Worthing, MD, chair of the American College of Rheumatology's Government Affairs Committee. The European Medicines Agency approved its first biosimilar in 2006. Since then, 23 such biosimilars have come on the market, at an average price of about 30% less than the reference product. Prices have dropped as much as 70% in countries in which national health care systems abandoned the reference product in favor of the competing biosimilar, Dr. Worthing said in an interview.

"But the U.S. doesn't have a national health care system, so it won't work like that here." In fact, he noted, brand-new data show that Medicare actually paid 22% more for the infliximab biosimilar Inflectra than it did for Remicade in the last quarter of 2016.

It's not immediately apparent why this is the case, but it's probably related to drug company discounts and rebates on these very expensive treatments. According to the report in Inside Health Policy, Janssen Biotech may have increased its discount to compete with Inflectra's launch price of 15% below Remicade's wholesale cost. Prices won't moderate as much in the United States as in the European Union until several biosimilars of the same class appear, Dr. Worthing said.

There have already been allegations that big pharma manipulates international and national pricing to reduce biosimilar competition.

In June, Russian biotech company Biocad filed a lawsuit in New York charging Roche/Genentech with price fixing. The suit alleges that the companies cut the cost of three cancer treatments (Avastin, Herceptin, and Rituxan/MabThera) in Russia, where Biocad markets biosimilars for each. At the same time, Biocad alleges, the companies raised U.S. prices on those products to make up for the money they were losing on the Russian market.

It's also unclear who would actually reap the financial rewards of a burgeoning biosimilar market in this country, said Jonathan Krant, MD, chief of rheumatology and chairman

Continued on following page

Vancomycin beats metronidazole for *C. diff* mortality

BY BIANCA NOGRADY
Frontline Medical News

Treating *Clostridium difficile* infection with vancomycin achieves the same recurrence rates as does treatment with metronidazole, but with a significantly lower 30-day mortality, new research suggests.

A retrospective, propensity-matched cohort study examined U.S. Department of Veterans Affairs health care system data from 47,471 patients with *C. difficile* infection who were treated with either vancomycin or metronidazole, according to a report published online in JAMA Internal Medicine.

"Current guidelines recommend metronidazole hydrochloride as initial therapy for most cases of mild to moderate CDI [*Clostridium difficile* infection]," wrote Vanessa W. Stevens, PhD, of Veterans Affairs Salt Lake City Health Care System, and her coauthors. "Although an early clinical trial found no difference in cure rates between vancomycin hydrochloride and metronidazole, subsequent observational data and clinical trials suggest that metronidazole is inferior to vancomycin for primary clinical cure, especially in severe cases."

Their study found patients treated with vancomycin had a similar risk of recurrence, compared with those treated with metronidazole (relative risk, 0.98; 95% confidence interval, 0.87 to 1.10), with an overall recurrence rate of 16%.

However, patients treated with vancomycin had a 14% reduction in 30-day mortality, compared with the metronidazole-treated group. This was after adjustment for factors such as comorbidity scores, hospitalization history, receipt of chemotherapy, receipt of immunosuppressive medication or proton pump inhibitor therapy in the prior 30-days, or antibiotic use on the day of diagnosis.

The 30-day mortality was not significantly different among patients with mild to moderate CDI, but there was a significant 21% reduction among patients with severe infection. The number needed to treat to prevent one death among patients with severe infection was 25 (JAMA Intern Med. 2017 Feb 6. doi: 10.1001/jamainternmed.2016.9045).

"This is the largest study to date to compare vancomycin and metronidazole in a real-world setting and one of the few studies focused on downstream outcomes of CDI," researchers reported.

The authors noted that, despite strong evidence and guidelines supporting the use of vancomycin for severe CDI – and the fact that 42% of episodes in the study were classified as severe – only 4%-6% of patients were prescribed vancomycin.

"Although the excess treatment costs of vancomycin relative to metronidazole and the concern for vancomycin-resistant Enterococcus will likely remain barriers, improved clinical cure and mortality rates may warrant reconsideration of current prescribing practices," they wrote. "One approach to minimizing the effects of increasing vancomycin use is to target vancomycin treatment to patients with severe disease."

The study was supported by researcher grants from the U.S. Department of Veterans Affairs. No conflicts of interest were declared.

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AGA Resources

AGA offers patient education materials to help you discuss *C. difficile* with your patients at http://www.gastro.org/patient-care/conditions-diseases/clostridium-difficile-infection.

Continued from previous page

of the department of medicine at Adirondack Health Systems in Saranac Lake, N.Y.

"I think most of the cost benefits will accrue to insurance plans and pharmacy managers, but maybe not to the patients themselves," he said in an interview. "The most important beneficiaries may not see a single penny of benefit."

It may be difficult to extrapolate the European economic experience into the U.S. health care market, but the safety record of its biosimilars is solid. None of the biosimilars approved in the E.U. have ever been recalled or removed from the European market because of regulatory or safety concerns.

Nonmedical switching raises concerns

Academic medical societies and clinicians interviewed for this article view the proposed approval pathway with cautious optimism. While acknowledging the potential benefit of reducing the costs of prohibitively expensive treatments, they uniformly insist that patient safety – not economic pressure – should be the driving force here.

"I was initially skeptical, and I do believe that we need very close pharmacovigilance in monitoring these for safety," said Gideon Smith, MD, PhD, a dermatologist at Massachusetts General Hospital, Boston. "But there has been huge uptake of these products in the E.U., and the data are so extensive that we can be reasonably confident these drugs are effective, and no good reason to believe the safety will be any different."

He is not as comfortable with the prospect of pharmacy-level substitution of an interchangeable biosimilar with the reference product – a feeling that other clinicians echoed.

The prospect of switching between products makes gastroenterologist Stephen Hanauer, MD, AGAF, nervous.

"In general, the GI field is OK with the idea of starting someone on a new prescription [of an interchangeable biosimilar], but not so much with the idea of switching around," said Dr. Hanauer, who is the Clifford Joseph Barborka Professor of Gastroenterology at Northwestern University, Chicago. "In these biologic compounds, very small differences can be amplified" and alter therapeutic response.

The possibility of switching from the reference to the biosimilar and maybe back again worries him. He hearkened back to the approval of Remicade, when patients who had taken it during clinical trials only were finally able to obtain it on the market. Dr. Hanauer explained that, "20% of them developed serum sickness reactions after the reexposure."

He also expressed some concern about quality control in international manufacturing plants, citing a 2005 epidemic of immune-mediated pure red cell anemia in patients who received an epoetin alfa biosimilar manufactured in Thailand. The prefilled syringes had an uncoated rubber stopper that apparently reacted with polysorbate 60 in the solution – an interaction that increased immunogenicity when the product was administered subcutaneously.

Dr. Smith concurred. "We know that some patients produce antibodies to biologics if they come on and off, and so we discourage that. The concern is that switching may lead to an increased rate of medication failure, if you have to switch back. This is especially troubling in the case of a hard-to-control patient with severe flares. If they're being well controlled on a medication, the last thing you want to do is change it for no good clinical reason. And we may well be forced to do that."

Neither the American Academy of Dermatology nor the AGA has a published stand on the FDA's proposed guidance for interchangeable biosimilars. The preliminary view of the American College of Rheumatology is a positive one, Dr. Worthing said. However, ACR feels pharmacy-level switching should be a joint, not unilateral, decision.

Bringing any biosimilar to market, though, takes a lot of money and a lot of time. And while companies are growing cell lines and producing new molecules that mimic existing treatments, science marches on, said Dr. Smith.

"If we keep dragging our feet on this issue, it might end up being a moot point," he said. Newer products are achieving better results, raising the bar for therapeutic success. An example is the monoclonal antibody secukinumab (Cosentyx), an inhibitor of interleukin 17A. In October 2016, late-breaking data released at the annual meeting of the European Academy of Dermatology and Venereology impressed the dermatology community. In psoriasis patients, the treatment maintained 90% skin clearance for 4 years in 66% of patients, and 100% clearance for 4 years in 43%.

Not only does this kind of efficacy provide symptomatic relief, it also prevents the expensive long-term morbidity associated with psoriasis, Dr. Smith said.

"Even if these new medications are considerably more expensive upfront than a biosimilar for an older drug, they may end up being less expensive in the long run."

Dr. Krant and Dr. Worthing had no financial disclosures. Dr. Smith has received grants from Allergan and Cipher Pharmaceuticals. Dr. Hanauer has received grants from numerous pharmaceutical companies that manufacture biologics.

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AGA CLINICAL PRACTICE UPDATE

Best practice advice on EBT use released

BY DEEPAK CHITNIS
Frontline Medical News

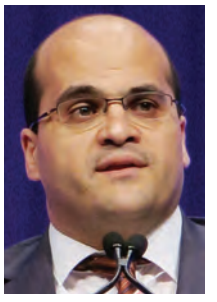
The AGA Institute has released a series of new best practice statements that gastroenterologists should use when considering a patient for endoscopic bariatric treatments or surgeries (EBTs).

"There is a need for less-invasive weight loss therapies that are more effective and durable than lifestyle interventions alone, less invasive and risky than bariatric surgery, and easily performed at a lower expense than that of surgery, thereby allowing improved access and application to a larger segment of the population with moderate obesity," wrote the authors of the expert review, led by Barham K. Abu Dayyeh, MD, of the Mayo Clinic in Rochester, Minn.

The report is in the March issue of Gastroenterology (doi: 10.1053/j.gastro.2017.01.035). "[EBTs] potentially meet these criteria and may provide an effective treatment approach to obesity in selected patients."

The best practice statements come from a review of relevant studies in the Ovid, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus databases, among others, that were published between Jan. 1, 2000, and Sept. 30, 2016.

EBTs should be used on patients who have already been unable to lose weight despite lifestyle interventions and more traditional weight loss methods. However, patients who undergo EBTs should also be placed on a weight loss regimen that includes diet, exercise, and lifestyle changes.



'There is a need for less-invasive weight loss therapies that are more effective and durable than lifestyle interventions.'

DR. ABU DAYYEH

In addition to being used for weight loss, these treatments can also be used to transition a patient to traditional bariatric surgery, or to lower a patient's weight so that they can undergo a different procedure unrelated to bariatric surgery.

Anyone being considered for EBT, or a weight loss regimen involving EBT, should be thoroughly evaluated for comorbidities, behavior, or medical concerns that could lead to adverse effects.

Any patients who are placed on EBT regimens should be followed up regularly by their clinicians to monitor their progress in terms of weight loss and the development of any adverse effects.

Should any adverse outcomes arise, alternative therapies should be implemented as soon as possible, Dr. Abu Dayyeh said.

Clinicians are advised to know the ins and outs of risks, contraindications, and potential complications related to EBTs before ever implementing them in their practice, let alone recommending them to a patient.

Finally, it's imperative that health care institutions with EBT programs make sure there are training protocols clinicians must stringently follow before being allowed to perform EBT procedures.

"Moving ahead, it will be important to better incorporate training in obesity management principles into the GI fellowship curriculum to have a more significant impact," the authors wrote, adding that it's important to study the "tandem and sequential use of a combination of EBTs and obesity pharmacotherapies in addition to a comprehensive life-style intervention program."

Dr. Abu Dayyeh disclosed relationships with Apollo Endosurgery, Metamodix, Aspire Bariatric, and GI Dynamics. Other coauthors also disclosed potential conflicting interests.

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Worsening type 2 diabetes may flag pancreatic cancer

BY NEIL OSTERWEIL
Frontline Medical News

AMSTERDAM – Incretin-based antidiabetic drugs do not appear to increase risk for pancreatic cancer, but the acute need for these drugs because of rapid worsening of type 2 diabetes may be a marker for early, occult pancreatic adenocarcinoma, investigators cautioned.

Results of a study of nearly 825,000 patients with type 2 diabetes in Belgium and northern Italy showed that patients who required a first-time prescription for an incretin-based antidiabetic drug had a 3.5-fold greater risk of being diagnosed with pancreatic cancer within 3 months, compared with patients who could be safely maintained on an oral noninsulin, nonincretin antidiabetic drug (NIAD), reported Alice Koechlin of the International Prevention Research Institute in Lyon, France, on behalf of coauthor Phillipe Autier, MD, also of the institute.

But the risk of cancer diminished over time, suggesting that there was no causal relationship between incretins and pancreatic cancer. Instead, the need for incretins signals a more severe presentation of diabetes that may be caused by an early, undetected pancreatic malignancy, she said.

"We think that, at the beginning, there is an asymptomatic pancreatic cancer, with no clinical findings, and its first health effects are to disturb glucose metabolism. Then patients are diagnosed with type 2 diabetes, they are prescribed antidiabetic drugs, and then, as the cancer progresses but is still asymptomatic, the diabetes is less well controlled, and the patients shift to incretins and insulin more rapidly. And when the symptoms [of cancer] appear, it is too late for treatment," Ms. Koechlin said at an annual congress sponsored by the European Cancer Organisation.

Incretin hormones stimulate the release of insulin from the pancreas. Incretin-based therapies such as dipeptidyl peptidase-4 inhibitors (DPP4 inhibitors, or gliptins) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), are generally held in reserve for patients with type 2 diabetes who have poor or inadequate glycemic control on oral agents such as metformin or the sulfonylureas.

Data from laboratory studies have suggested that incretins in general, and GLP-1 RAs in particular may increase risk of pancreatic cancer because of their direct action on the gland, Ms. Koechlin said.

As a part of postmarketing studies of the GLP-1 RAs requested by the European Medicines Agency (EMA), the investigators drew data from the Belgian Cancer Register on 11 million people in Belgium and from a registry maintained by the University of Milano-Bicocca, which covers approximately 10 million people in the Lombardy region of Italy.

They identified patients with type 2 diabetes who received a first prescription of an incretin drug or NIAD from January 2008 through the end of 2013 in Belgium, and through the end of 2012 in Italy.

They found that at first, incretin use did indeed appear to be associated with risk of pancreatic cancer, compared with NIAD use. Hazard ratios for cancer with incretin were 2.12 in Belgium (95% confidence interval, 1.60-2.81) and 2.17 (95% CI, 1.50-3.13) in Lombardy. 1.71-2.67).

When they looked at the risk of cancer from incretin use over time, however, they found that the risk was highest at 3.5-fold, compared with NIAD use, within 3 months of starting a first prescription, but diminished to 2.3-fold during months 3-6, 2-fold for months 6-12, and 1.7-fold after the first year. "This is not compatible with a causal relationship, because if there was a causal relationship we would observe a small risk for shorter duration of use, and higher risk for higher duration of use," she said.

They also looked at the relationship between a first prescription for insulin during follow-up, and saw significant increases in cancer risk, compared with patients who did not require insulin, with an HR in Belgium of 6.61 (95% CI, 5.63-7.77), and 7.46 (95% CI, 6.00-9.35) in Lombardy.

The perceived association between incretin drugs and cancer risk, therefore, may be due to "protopathic" or "reverse causation" bias, Ms. Koechlin said.

The study was sponsored by Sanofi. The investigators and Dr. Banks reported no conflicts of interest.

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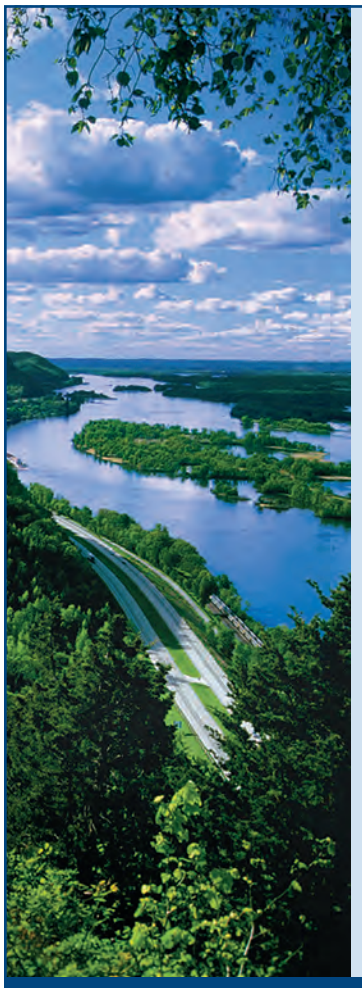

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PRACTICE MANAGEMENT TOOLBOX:

Bundled payment for gastrointestinal hemorrhage

BY SHIVAN J. MEHTA, MD, MBA

The Medicare Access and Chips Reauthorization Act (MACRA) is now law; it passed with bipartisan, virtually unanimous support in both chambers of Congress. MACRA replaced the Sustainable Growth Rate formula for physician reimbursement and replaced it with a pathway to value-based payment. This law will alter our practices more than the Affordable Care Act and to an extent not seen since the passage of the original Medicare Act. Practices that continue to hang on to our traditional colonoscopy-based fee-for-service reimbursement model will increasingly be marginalized (or discounted) by Medicare, commercial payers, and regional health systems. To thrive in the coming decade, innovative practices will move toward alternative payment models. Many practices have risk-linked bundled payments for colonoscopy, but this step is only for the interim. Long-term success will come to practices that understand the implications of episode payments, specialty medical homes, and total cost of care. Do not wait for the finances to magically appear – start now to build infrastructure. In this month's article, Dr. Mehta provides a detailed description of how a practice might construct a bundled payment for a common inpatient disorder. No one is paying for this yet, but it will come. Now is not the time to be a "WIMP" (Gastroenterology. 2016;150:295-9).

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

In January 2016, the Centers for Medicare & Medicaid Services (CMS) launched the Comprehensive Care for Joint Replacement (CJR) model. This payment model aims to improve the value of care provided to Medicare beneficiaries for hip and knee replacement surgery during the inpatient stay and 90-day period after discharge by holding hospitals accountable for cost and quality.[1] It includes hospitals in 67 geographic areas across the United States and marks the first time that a postacute bundled payment model is mandatory for traditional Medicare patients. Although this may not seem to be relevant for gastroenterology, it marks an important signal by CMS that there will likely be more episode-payment models in the future.

It is well known that the government and policymakers have been promoting a shift to value-based reimbursement, most notably through the Affordable Care Act. In 2015, the Department of Health and Human Services announced goals for shifting Medicare reimbursement from fee for service to payments that are based on the value of care.[2] In addition, the Medicare Access and CHIP Reauthorization Act consolidated pay-for-performance programs for physician reimbursement and will direct more rewards and penalties for alternate payment models.[3] Most of the public discussion has been around outpatient-focused models such as Accountable Care Organizations, but postacute bundled payments have also been proliferating across the country, initially through voluntary participation by hospitals.


DR. MEHTA

Gastroenterologists have not been primary drivers or participants in these models, but gastrointestinal hemorrhage is included as 1 of the 48 clinical conditions for the postacute bundled payment program. In addition, CMS recently announced that clinical episode-based payment for GI hemorrhage will be included in hospital inpatient quality reporting (IQR) for fiscal year 2019.[4] This is an opportunity for the field of gastroenterology to take a leadership role in an alternate payment model as it has for colonoscopy bundled payment,[5] but it requires an understanding of the history of postacute bundled payments and the opportunities for and challenges to applying this model to GI hemorrhage. In this article, I will describe insights from our health system's experience in evaluating different postacute bundled payment programs and participating in a GI bundled payment program.

Inpatient and postacute bundled payments

A bundled payment refers to a situation in which hospitals and physicians are incentivized to coordinate care for an episode of care across the continuum and eliminate unnecessary spending. In 1983, Medicare initiated a type of bundled payment for Part A spending on inpatient hospital care by creating prospective payment that is based on diagnosis-related groups (DRGs). This was a response to the rising cost of inpatient care resulting from retrospective payment that is based on hospital charges. Because hospitals would get paid the same amount for similar conditions, it resulted in shortened length of stay and reduction in the rise of inpatient costs, along with no measurable impact on quality of care.[6] This was followed by prospective payment for outpatient hospital fees and skilled nursing facility (SNF) care as a result of the Balanced Budget Act of 1997. Medicare built on this by bundling physician and hospital fees through demonstration projects in coronary artery bypass graft surgery from 1991 to 1996 and orthopedic and cardiovascular surgery from 2009 to 2012, both resulting in reduced costs and no measurable impact on quality.

Content from this column was originally published in the "Practice Management: The Road Ahead" section of Clinical Gastroenterology and Hepatology (2016;14:1681-4).

The Bundled Payment for Care Improvement (BPCI) program built on these results in 2013 by expanding to include Part A and B services rendered up to 90 days after discharge, and as of January 2016, it includes 1,574 participants across the country. On a voluntary basis, hospitals, physician groups, and postacute providers and conveners were able to participate in 1 of 4 bundled payment models that were anchored on an inpatient for any of 48 clinical conditions that were based on MS-DRG (Table 1).

- Model 1 defined the episode as the inpatient hospital stay and bundled the facility and physician fees, similar to prior demonstration projects.
- Model 2 is a retrospective bundled payment for Part A and B services in the inpatient hospital stay and up to 90 days after discharge.
- Model 3 is a retrospective model that starts after hospital discharge and includes up to 90 days. (Models 1-3 maintain the current payment structure and retrospectively compare the actual reimbursement with target values that are based on historical data for that hospital with a 2%-3% payment reduction.)
- Model 4 makes a single, prospectively determined global payment to a hospital that encompasses all services during the hospital stay.

Orthopedic bundles have had the greatest adoption, and this is reflected by the CJR model, which includes hospitals in 67 geographic areas across the country for hip and knee replacement surgery, and is similar to model 2 of BPCI. These bundled payment models have also been proliferating in the commercial insurance markets, because payers have value-based goals similar to Medicare, and there are economies of scale for both providers and payers.

Table 1. Medicare BPCI improvement models

	Model 1	Model 2	Model 3	Model 4
Episode	All DRGs; all acute patients	Selected DRGs; hospital plus postacute period	Selected DRGs; postacute period only	Selected DRGs; hospital plus readmissions
Services included in the bundle	All Part A services paid as part of the MS-DRG payment	All nonhospice Part A and B services during the initial inpatient stay, postacute period, and readmissions	All nonhospice Part A and B services during the postacute period and readmissions	All nonhospice Part A and B services (including the hospital and physician) during initial inpatient stay and readmissions
Payment	Retrospective	Retrospective	Retrospective	Prospective

Source: www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2015-Fact-sheets-items/2015-08-13-2.html

Opportunities in inpatient and postacute bundled payments

Participation in bundled payments requires a new set of analytic and organizational capabilities.

- The first step is to identify the patient population on the basis of inclusion and exclusion criteria and to measure the current cost of care through external claims data and internal hospital data.

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This includes payments for hospital inpatient services, physician fees, postacute care, readmissions, other Part B services, and home health services. The biggest opportunity for postacute bundles is shifting site of service from postacute care to lower-cost settings and reducing readmission rates.

- Subsequently, they need to identify areas of opportunity to reduce expenditure, while also demonstrating consistent or improved quality and outcomes.
- On the basis of this, the team can identify variation in care within the cohort and in comparison with benchmarks across the country.
- After identifying areas of opportunity, the team needs to develop strategies to improve value such as care pathways, information technology tools, care coordination, and remote services.

Of the 48 clinical conditions in BPCI, 4 could be described as related to GI: esophagitis, gastroenteritis, and other digestive disorders (Medicare Severity–Diagnosis Related Group [MS-DRG] 391, 392); gastrointestinal hemorrhage (MS-DRG 377, 378, 379); gastrointestinal obstruction (MS-DRG 388, 389, 390); and major bowel procedure (MS-DRG 329, 330, 331). After evaluating the GI bundles, it was apparent that these were created for billing purposes and were not clinically intuitive, which is why our institution immediately excluded the broad category of esophagitis, gastroenteritis, and other digestive disorders. GI obstruction and major bowel surgery relate to the care of gastroenterologists, but surgeons are typically primary drivers of care for these patients. Thus, we believed that GI hemorrhage was most appropriate because gastroenterologists drive care for this condition, and there is substantial evidence about established guidelines and pathways during this episode.

Bundled payment for gastrointestinal hemorrhage

We built a multidisciplinary team of physicians, data analysts, clinical documentation specialists, and care managers to start developing a plan for improving the value of care in this population. This included data about readmissions and site of postacute care for this population, which were supplemented by chart review of financial outliers and readmissions. We quickly learned about some of the challenges to medical bundles and the GI hemorrhage bundle in particular. It is difficult to identify these patients early in the hospital stay because inclusion is based on a billing code. Many of these patients also have cardiovascular disease, cancer, or cirrhosis, which makes it hard to identify which patients will end up with primary GI hemorrhage coding until after the patient is discharged. They are also on many different inpatient services; in our hospital, there were at least 12 different admitting services. In addition, almost one-third of the patients actually had an admission before this hospitalization, often for different clinical conditions.

Most importantly, it was very challenging to develop protocols to improve the value of care in this population. Most of the patients had many comorbid conditions, so a GI hemorrhage pathway alone would not be sufficient to alter care. The two main areas of opportunity for cost savings in postacute bundled payments are postacute site of service and readmissions, both of which are hard to change for medical GI patients. For medical patients, they have many comorbidities before admission, so postacute site of service is typically driven by which site they were admitted from. This is different from surgical patients who are in SNF or rehabilitation facilities for limited time frames, and there may be more discretion to shift to lower cost settings. In addition, readmissions have not been studied much in GI hemorrhage, so it is not clear how to improve them. On the basis of these factors and the limited sample size for this condition, our health system opted to stop taking financial risk for this population.

Future opportunities for gastroenterology

However, the latest CMS Inpatient Prospective Payment System rule describes the implementation of a new quality metric for hospital IQR called the Gastrointestinal Hemorrhage Clinical Episode-Based Payment. This would hold hospitals accountable for the cost of care for GI hemorrhage admissions plus the 90 days after discharge, similar to model 2 of BPCI. This announcement, as well as the launch of mandatory orthopedic bundles, demonstrates that hospital reimbursement is shifting toward an expansion of bundled payments to include the postacute time frame. This is manifested in postacute bundles, episode-based payment, and readmission penalties. This reignited our GI hemorrhage episode team's efforts, but with a broader purpose.

Gastroenterologists can take a leadership role in responding to episode-based payments as a way for us to demonstrate value in our collaboration with hospitals, health systems, and payers. The focus on cardiovascular disease as part of readmission penalties and core measures has allowed our cardiology colleagues to partner closely with service lines, learn about episode-based care, and garner resources to build and lead disease and episode teams. Because patients do not fit into the different clinical areas in mutually exclusive categories, we will need to collaborate with other specialties to care for the overlap with other conditions. Many heart failure and myocardial infarction patients will get readmitted for GI hemorrhage, and many GI hemorrhage patients will have concomitant cardiovascular disease or cancer. This suggests that future strategies need to integrate efforts of service lines and that there is greater opportunity for gastroenterologists than just the GI bundles.

Gastroenterologists should also participate in a proactive way. Any new payment mechanism will have some flaws in implementation, so it is more important to do what is right from a clinical standpoint rather than focusing too much on the specific billing code or payment model. These models are evolving, and we have an opportunity to have impact on future implementation. This starts with identifying and including patients from a clinical perspective rather than focusing on specific insurance types that participate in bundled payments. Some examples to improve the value of care in GI hemorrhage include creating evidence-based care pathways that span the episode of care, structured documentation after endoscopy for risk stratification, integrating pathways into the workflow of providers through the electronic health record, and increased coordination between specialties across the continuum of care. Other diagnoses that might be included in future bundles include cirrhosis, bowel obstruction, and inflammatory bowel disease. We can also learn from successful efforts in other clinical specialties that have identified variations in care and implemented a multi-modal strategy to improving care and measuring impact.

Take-away points:

1. Postacute bundled payments hold hospitals accountable for the cost of care during hospitalization and in the 90 days post discharge.
2. The bundled payment for gastrointestinal hemorrhage is an opportunity for gastroenterologists to take a leadership role in bundled payments.
3. Challenges in responding to this payment model include difficulty identifying patients in the hospital, the complexity and comorbidities of patients, and limited opportunities to reduce utilization.

References

1. Mechanic, R.E. Mandatory Medicare bundled payment: Is it ready for prime time? N Engl J Med. 2015;373[14]:1291-3.
2. U.S. Department of Health and Human Services. Better, smarter, healthier: In historic announcement, HHS sets clear goals and timeline for shifting Medicare reimbursements from volume to value. January 26, 2015. Available from: http://www.hhs.gov/about/news/2015/01/26/better-smarter-healthier-in-historic-announcement-hhs-sets-clear-goals-and-timeline-for-shifting-medicare-reimbursements-from-volume-to-value.html. Accessed June 28, 2016.
3. Patel, K., Presser, E., George, M., et al. Shifting away from fee-for-service: Alternative approaches to payment in gastroenterology. Clin Gastroenterol Hepatol. 2016;14[4]:497-506.
4. Medicare FY 2016 IPPS final rule. Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2016-IPPS-Final-Rule-Home-Page.html. Accessed June 28, 2016.
5. Ketover, S.R. Bundled payment for colonoscopy. Clin Gastroenterol Hepatol. 2013;11[5]:454-7.
6. Coulam, R.F., Gaumer, G.L. Medicare's prospective payment system: a critical appraisal. Health Care Financ Rev Annu Suppl. 1991:45-77.

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