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WHO'S IN THE ROOM?

Examining anesthesiologist assistance in routine endoscopy and colonoscopy procedures

By Jeff Mandel, MD, MS, and John Vargo, MD, MPH, AGAF.

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In this issue

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Note From the Editor

It's finally summer and as the temperature heats up, so does this issue of *AGA Perspectives*, which touches on a variety of "hot" and rapidly evolving areas in digestive diseases today. Our opening debate examines the ever-provocative topic of the role of the anesthesiologist in routine gastroenterology procedures. Important pro and con points are made in this long-standing area of controversy by Dr. Jeff Mandel from the anesthesiology perspective and Dr. John Vargo from the gastroenterology perspective.

Another "red hot" issue in GI is the ongoing concern of proton pump inhibitor side effects and recent high profile media attention to this. This has led to considerable consternation among both patients and physicians, as well as confusion. Dr. Paul Moayyedi provides a helpful perspective to our readership on how to interpret the recent studies that have drawn so much attention.

Other rapidly evolving areas addressed in this issue include advances in the treatment of HCV genotype 3 by Drs. Rama Behara and Nancy Reau, new treatment options for IBS-D by Dr. Ron Schey and advances in gut microbiome research by Dr. Rob Knight. A common clinical conundrum is timing and need, if any, of ERCP in patients with suspected choledocholithiasis. Dr. B. Joseph Elmunzer provides an evidence-based approach to this problem in his article.

Nutrition is an area that has been underemphasized in recent years in the world of gastroenterology. Dr. Octavia Pickett-Blakely reminds us that digestive disease treatment encompasses nutrition as well, and emphasizes the need to for both the practicing community and training programs to rethink our approach to this area.

It is also with great pleasure that we introduce you to our new AGA President, Dr. Timothy Wang, who was sworn in earlier this year, in this June/July issue of our magazine.

To learn more about these and other *AGA Perspectives* articles, make sure to visit our online home for the magazine, agaperspectives.gastro.org.

Best,

Gary W. Falk, MD, MS, AGAF
EDITOR
@DrGaryFalk

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WHO'S IN THE ROOM?

Examining anesthesiologist assistance in routine endoscopy and colonoscopy procedures

View from an Anesthesiologist

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Dr. Mandel serves on the board of directors for the Society for Technology in Anesthesia.

The question of who may administer endoscopic sedation has burned for over a decade, but recent developments have fanned the flames again. The approval by FDA of the SedaSys system and its subsequent withdrawal from the market has increased the heat, but not the light, surrounding this controversy. I am hopeful that this pro-con discussion can facilitate a cooling of passions. There is not a clear answer to "what is best for the patient." If more patients undergo screening colonoscopy because they can get anesthesiologist-administered propofol, this is good. If the cost of anesthesiologist-directed propofol causes patients to avoid colonoscopy due to increased co-payments, this is bad. Given the low rate of complications of endoscopic sedation and the lack of an objective standard for evaluating the quality of endoscopic sedation, it is unlikely that we will have high-level evidence that answers the question of "what is safe", much less "what is good". So, let us turn to what is possible.

As an anesthesiologist who is actively involved in the development of automated delivery of propofol, I am often confronted by colleagues who tell me that I'm trying to put them out of a job. "It is not a job that you have," I tell

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View from a Gastroenterologist

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Dr. Vargo has no conflicts to disclose.

Anesthesiologist-directed sedation for ambulatory endoscopic procedures has enjoyed an unparalleled and unbridle growth in recent years. Between 2003 and 2009, payments for anesthesiologist-directed sedation tripled from just under $400 million to 1.3 billion. This dramatic upsurge was driven not by increased cost but by increased utilization, which occurred almost exclusively in the commercial payor sector. Liu and colleagues estimated that of the $1.3 billion being paid for anesthesiologist-directed sedation, only $200 million was earmarked for high-risk patients.[1] As gastroenterologists evolve from fee-for-service to value-based care, and eventually to a more risk-based landscape, we must ask ourselves, what are the prospects for anesthesiologist-directed sedation for low-risk ambulatory endoscopic procedures such as colonoscopy in healthy patients? Please keep in mind that colonoscopy relative value units continue to erode and the work associated with delivering procedural sedation has been pared from the procedural codes. When we critically dissect the value proposition for anesthesiologist-directed sedation in this scenario, what do we find? The results may surprise and scare you.

Does anesthesiologist-directed sedation lead to improvements in the outcomes of ambulatory endoscopic procedures? Dominitz et al. utilized a sample of Medicare administrative claims

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them, "and it is not a job that you want." According to the Department of Labor, there are about 30,000 anesthesiologists employed in the U.S. The number of colonoscopies performed annually in the U.S. may exceed 30 million. If 10 percent of U.S. anesthesiologists staff 50 cases a day, five days a week, 50 weeks a year, we could achieve 100 percent coverage. I'll leave the discussion regarding the cost of this to others, but it is unrealistic to propose 100 percent of cases be performed under a traditional anesthesia care model. Therefore, we must look to other models.

A number of alternative models have been proposed that shift administration of propofol from anesthesia providers to gastroenterologists and nurses who are not "trained in the administration of general anesthesia." These models presume that a gastroenterologist can safely administer propofol to a subset of patients. While this approach has been validated, it has not been widely embraced. I'm not questioning John Vargo's or Doug Rex's ability to deliver propofol, but there are factors that will hinder wide adoption of propofol administration by nonanesthesiologists.

First, the gastroenterologist providing propofol sedation will almost certainly do so under a protocol crafted by a committee. Most committees will stick to that which can be easily measured — milligrams of propofol, possibly infusion rates. Since there is no readily available technology for real-time measurement of propofol blood levels, nor are there target-controlled infusions that could estimate these levels available in the United States, effect site concentrations will not be part of the protocol. Using drug administration, rather than effect site concentration, increases the uncertainty in propofol dosing by a factor of two.[2]

Data from my research group suggests a range of effect site levels required for endoscopy varies by a factor of four.[3] These uncertainties cascade, so even if the committee would agree that the propofol limit should be based on some statistical measure of anesthesiologist practice, this number would be far from the target in many patients. A more likely outcome would be that the committee would choose to limit the dose based on a feared complication such as airway obstruction. Our data from studies of drug-induced sleep endoscopy suggests that the probability of airway collapse at effect site concentrations below 2 µg/ml is negligible.[4] The problem is that this is 50 percent of the median effect site concentration in our endoscopy cohort, and given the skewed nature of the distribution, it is likely that a policy that tried to avoid obstruction would fail to achieve unresponsiveness in many patients and would fail to produce amnesia in some patients. Anesthesiologists deal with this uncertainty by adjusting the dose based on observation of the response, and gastroenterologists could likely learn this skill but will be restricted by hospital policy from exceeding this fixed dose. At my institution, midazolam dose in the endoscopy unit

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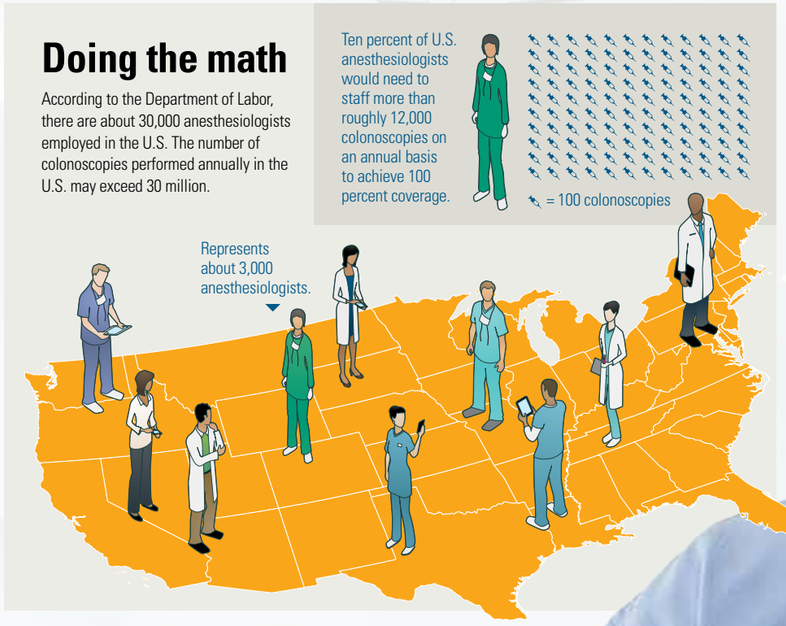

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submitted for 328,177 adults undergoing outpatient colonoscopy.[2] The authors found no difference in the polyp diagnosis rates between anesthesiologist-directed sedation and endoscopist-directed sedation (OR 1.04; 95 percent CI: 0.99,1.09).[2] Recent studies have shed a sobering light on the notion that anesthesiologist-directed sedation is a safer avenue for ambulatory endoscopic sedation. Please keep in mind that the use of targeted moderate sedation allows feedback from our patients. A signal of discomfort from a patient during colonoscopic insertion should trigger not only a reassement of the current depth of sedation, but also whether the technique of the endoscopist should be altered due to instrument looping or over insufflation.

At this juncture, let's remind ourselves that propofol has no analgesic properties. Hence, anesthesiologist-directed sedation blows past the moderate sedation mile marker and into deep sedation or general anesthesia to make up for this shortfall: There is no patient feedback to noxious stimuli.

Korman et al. utilized a colonoscopy force-monitor system to access the physics of colonoscopic insertion/withdrawal in a case-control study pitting monitored anesthesia care against moderate sedation with an opioid and benzodiazepine.[3] The authors found that the maximum torque, push and pull force were significantly higher in the monitored anesthesia care (MAC) group. Although the authors did not find an association between higher force application and adverse events, they pointed out that the forces generated in some of the MAC group cases exceeded the thresholds needed to generate perforations and tears in cadaveric and surgical specimens.[4] The authors also found that MAC significantly decreased the overall examination time. Is the augmented force application an appropriate price to pay for reducing the procedure time by a couple of minutes?

Wernli et al. conducted a prospective cohort study of 3,168,228 colonoscopy procedures from an administrative claims database to determine the 30-day complication profile.[5]

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For colonoscopy, when compared to endoscopist-directed sedation, there was no safety benefit for anesthesiologist-directed sedation.

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is restricted to a maximum of 10 mg by a policy that has not been revised since 1986, and there is no reason to suspect that propofol will be any different.

A second factor is the need to have anesthesiologist backup for a subset of patients. Again, a committee will decide the criteria comorbidities, history of difficulty with sedation, current drug use etc. Can we predict those patients who will fail to achieve sedation under our policy? Our data suggests not. When assessing the actions of experienced certified registered nurse anesthetist providers, we found that only 36 percent of the variability in propofol administration was programmed prior to initiation of endoscopy. We react far better than we predict. Can we predict which patients will experience airway obstruction? In our experience with drug-induced sleep endoscopy in patients with severe obstructive sleep apnea, we could not predict whether airway maneuvers would be required. If a model that utilizes anesthesiologists for patients predicted to exceed the protocol dose or predicted to have complications (such as obstruction) allocates too many patients to the wrong pathway, it will fail. If there is a job I would like less than staffing 50 colonoscopies every day of my life, it is one where I am constantly running from room to room trying to deal with inadequate sedation and respiratory arrests (with the ratio determined by a committee over which I had no influence). Given these issues, it is likely that many centers will find that models that attempt to cherry pick easy cases for gastroenterologist-directed propofol with an anesthesiologist available for the hard ones will find staff retention problematic.

Is there an alternative? My group has described approaches to pharmacokinetic control of propofol that simplify the task of the anesthesiologist, permitting a different staffing model, perhaps 1:3[5,6]. Such a model would likely address both the manpower and cost issues associated with endoscopic sedation. Of course, this will require buy-in from third-party payors, professional organizations and hospital committees, assuming we can gain FDA approval and attract investors after what happened with SedaSys. Maybe our little brush fire isn't so bad after all. ■

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After adjusting the multivariate logistic regression model for age, gender, Charlson comorbidity index, geographic region and polypectomy status, the authors found that anesthesiologist directed sedation (ADS) was associated with a 13 percent higher risk of any complication studied within the 30-day window (95 percent CI:1.12,1.14). This included perforation, bleeding, abdominal pain, complications secondary to anesthesia, stroke and other central nervous system events. In fact, there was no complication subcategory that was reduced in association to ADS. In the previously mentioned study by Dominitz *et al*., there was no difference in the rates of bleeding, perforation, emergent hospitalization or emergency room visit within 30 days. In a retrospective cohort study of 1.38 million upper endoscopy and colonoscopy procedures in the Clinical Outcomes Research Initiative National Endoscopic Database, a composite of serious adverse events was compared between ADS and endoscopist-directed sedation utilizing a propensity analysis.[6] For colonoscopy, when compared to endoscopist-directed sedation, there was no safety benefit for anesthesiologist-directed sedation (OR 0.93, 95 percent CI: 0.82,1.06). For upper endoscopy however, the propensity adjusted risk for serious adverse events was higher for anesthesiologist-directed sedation (OR 1.33; 95 percent CI: 1.18, 1.50). The increased risk was present for patients who were classified as either ASA I/II or III.

One of the purported benefits of ADS is theorized to be improved patient satisfaction, which will, in turn, lead to greater acceptance of procedures such as a screening colonoscopy. Since there are no randomized controlled trials comparing ADS to GI-administered sedation, we will need to extrapolate somewhat. In the meta-analysis of McQuaid and Laine, patient satisfaction for propofol versus and benzodiazepine and opioid did find an advantage for the former (RR 0.90; 95 percent CI:0.83, 0.97), but it is important to point out that the propofol in these studies was administered under the direction of the endoscopist.[7]

And so, we are left in a quandary. We have no direct comparative data between anesthesiologist- and gastroenterologist-directed sedation. Unfortunately, we may never see that study completed. However, a surging tide of evidence shows that there is at best no safety benefit with ADS and no improvement in polyp detection. Additionally, if we are to believe that gastroenterologist-directed propofol sedation carries with it the same outcomes as anesthesiologist-directed sedation, the improvement in patient satisfaction is modest at best. We are then left with sedation practice that probably improves throughput but has a huge cost from payor perspective: a cost that is in the regulatory crosshairs and is ripe for reduction and curtailment. ■

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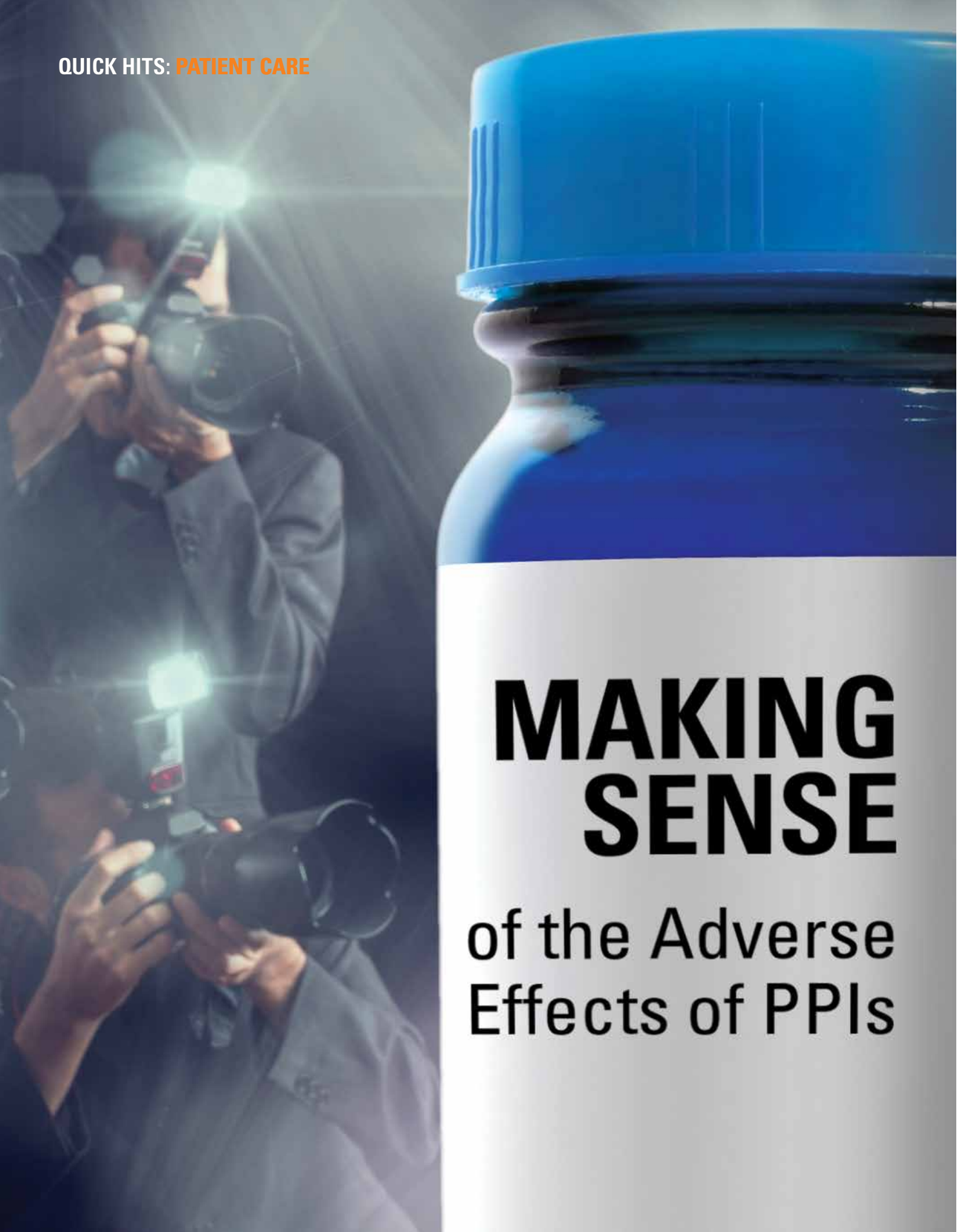

MAKING SENSE of the Adverse Effects of PPIs

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Dr. Moayyedi has no conflicts to disclose.

The science we conduct often reflects the society we live in. One phenomenon of current society is the rise of the reality television show. Participants are promised instant media fame without having to struggle through acting school. I worry that this has rubbed off on some of the studies we now conduct. Sir Richard Doll and Austin Hill, the architects of modern epidemiology, realized that it was hard for epidemiology to prove or disprove anything. Their studies were driven by clear hypotheses as some took five to 10 years to complete. Furthermore, their landmark paper on smoking and lung cancer devoted over a page of discussion as to why the observed association of an odds ratio greater than 10 of lung cancer in smokers may not be causal.[1]

This scientific version of the reality TV show is exemplified by some studies linking proton pump inhibitors (PPIs) to a variety of diseases. PPIs have been associated with GI infections (including *Clostridium difficile*), pneumonia, bone fractures, pernicious anemia, interactions with clopidogrel and heart disease. To this list we can now add chronic renal disease and dementia.[2,3] When a drug is associated with a long list of unrelated bad consequences it usually turns out that most, if not all, of these associations are not causal. This phenomenon was noted over 50 years ago but seems to have been forgotten by modern epidemiologists in the pursuit of the quick high-impact paper.[4] Indeed, there are a number of properties you can look for in an epidemiological study to try and determine whether the association might be causal. The first and most important is the strength of the association.

An old-school epidemiologist would never wake up for an odds ratio (OR) of less than two (to paraphrase the supermodel Linda Evangelista). None of the many papers reporting on the risks of PPIs have reported an adjusted OR greater than two. I am not saying that these studies should not be published but it is important that the authors emphasize that a strong association is more likely to be causal whereas a weak association is usually due to confounding factors. This is the most likely explanation for the myriad diseases that PPIs apparently "cause." Every study has shown that sicker patients tend to be prescribed PPIs.[5] They go to the doctor more often and at some point they will be prescribed these drugs if they complain of upper GI symptoms. Sick patients tend to develop other illnesses and so PPIs will be associated with about any disease you can imagine in a database. Patients on PPIs are also more likely to have diabetes mellitus and chronic obstructive pulmonary disease, and it is only a matter of time before you see papers reporting that PPIs "cause" these diseases as well.[5] An indicator that this is likely to be the case is that the unadjusted OR becomes much more attenuated when adjusting for confounding factors. For example, in the chronic kidney disease paper[2] the OR equals 1.76 (95 percent CI = 1.13 to 2.74) in the initial analysis but fell to 1.16 (95 percent CI = 1.09 to 1.24) in a propensity matched analysis in a replication cohort. This study could not identify all confounding factors, as it was not designed to test this specific hypothesis. It is very likely that if the authors could adjust for all known and unknown confounding factors, it would fall further and would no longer be statistically significant. This phenomenon is seen in nearly all papers of adverse events associated with PPI therapy but it is not mentioned as the likely explanation for the observed association in any study.[5] Dose response is another factor to look for and is rarely seen, although there are exceptions.[2,3,5] Authors do focus on biological plausibility, but I find this criterion very unhelpful as you can make a "biologically plausible" explanation for anything in modern medicine.

Sick patients tend to develop other illnesses and so PPIs will be associated with about any disease you can imagine in a database.

Surely it is important to know the possible risks of any drug, even if the most likely explanation is confounding factors. The reason for my rather churlish comments above, however, is that I spend a good deal of time explaining these issues to patients every time one of these associations hits the press. Last week, I counted 15 patients that I gave an explanation to (at their request) and each took five to 10 minutes. I calculated I could have seen seven extra patients if I had not had to explain what are likely to be spurious results. When you magnify this across North America, this is a significant burden on the GI health-care community that is of uncertain benefit. The only benefit this does have is that it is another opportunity to discuss with the patient about stopping their PPI therapy, as there are a significant proportion of patients that are on these drugs unnecessarily. However, if the patient has significant reflux symptoms or is at a major risk of GI bleed, the benefits of these drugs clearly outweigh any risks. This is because even in the unlikely event these associations are causal, the impact would be very small. We calculated that you would need to treat more than 1,000 patients for one to develop a fracture that would not have occurred anyway.[6]

We live in an instant gratification age. Sadly, this is sometimes reflected in the science that we produce, which makes it very difficult for the general clinician to make sense of the data. I must emphasize some of the papers in this space are well done and thoughtful, but many pay too little attention to why the associations they are reporting may not be causal and are too ready to jump to conclusions that are not supported by the data.[2] Sir Richard Doll would have been saddened by how the discipline he informed has been so sensationalized. Then again, he probably would not have liked "Keeping Up With the Kardashians." ■

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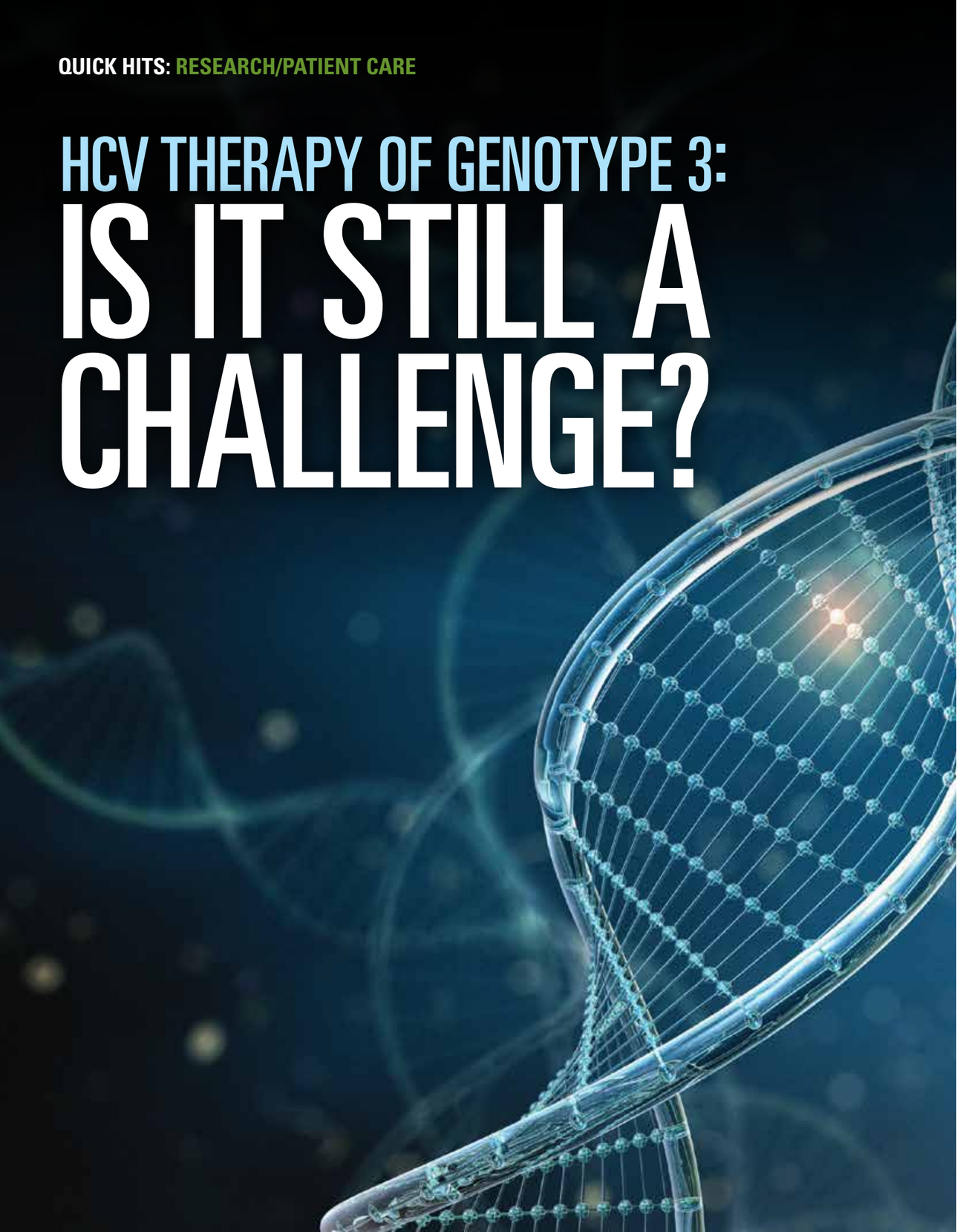
HCV THERAPY OF GENOTYPE 3: IS IT STILL A CHALLENGE?



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Dr. Reau has advised for Abbvie, Gilead, BMS, Merck and Intercept, and has received research support from Abbvie and Gilead. She serves on the AGA Education and Training Committee.

Hepatitis C genotype 3 accounts for 30 percent of all infections secondary to hepatitis C and is the second most common genotype worldwide, behind genotype 1. Estimates report that in the U.S., it accounts for 8 to 13 percent of infections. Historically, genotype 3 has been uniquely challenging to manage in large part due to lower response to therapy combined with high rates of steatosis, fibrosis progression and a disproportionately high rate of hepatocellular carcinoma. With the launch of the first wave of interferon-free treatment, many of the direct-acting antivirals (DAA) had higher overall sustained virologic response (SVR) to genotype 3 but did not compare to the SVR rate for treatments approved for genotype 1. Thus, recent drug development has focused on pan-genotypic agents to equalize efficacy across all genotypes.

For decades, genotype 3 had been associated with longer treatment and poorer results. Previously, genotype 2 and 3 had been grouped together in management as both responded to interferon-based therapy with higher SVR rates compared to genotype 1. However, several experts suggested separating the genotypes in light of different SVR rates as pegylated interferon (PEG-IFN) plus ribavirin was achieving SVR rates as high as 93 percent for genotype 2 compared to 65 to 80 percent for genotype 3. With the approval of the first DAAs — telaprevir and boceprevir — treatment efficacy significantly improved in HCV genotype 1 patients but had no impact on genotype 3.

Since then, several all-oral regimens have been approved for the treatment of HCV, many of which have efficacy against genotype 3 infection, including sofosbuvir (a nonstructural protein 5B inhibitor) plus ribavirin for 24 weeks as demonstrated in the FISSION, FUSION, POSITRON and VALENCE trials and more recently daclatasvir (nonstructural protein 5A inhibitor) plus sofosbuvir. Tolerability and efficacy improved dramatically, but SVR rates still failed to achieve rates similar to those with other genotypes, especially in challenging populations such as those with cirrhosis. Strategies to improve viral eradication included the addition of PEG-IFN, extension of therapy to 24 weeks and the addition of ribavirin, yet real-world data showed that SVR rates often fell below 90 percent and below 80 percent in those with more advanced disease. The recent push to develop pan-genotypic regimens with simple algorithms is erasing this gap.

On June 28, 2016, FDA approved the pan-genotypic, fixed-dose combination of sofosbuvir/velpatasvir for the treatment of HCV. Given once daily for 12 weeks despite genotype, this is again a major advance for individuals with hepatitis C, especially those with genotype 3.

The ELECTRON-2 trial investigated the use of the NS5A inhibitor velpatasvir, with sofosbuvir and demonstrated a 96 to 100 percent SVR12 rate in genotype 3 treatment-naïve patients without cirrhosis. This success was further supported in the Phase 3 ASTRAL-3 trial, which revealed a 95 percent SVR 12 using the combination of sofosbuvir and velpatasvir for 12 weeks in 277 treatment-naïve and experienced genotype 3 patients, including 30 percent with cirrhosis.

This regimen was superior to sofosbuvir and ribavirin for 24 weeks, which achieved SVR in only 80 percent of 275 subjects. Other promising pan-genotypic combinations include the nonstructural protein 5A inhibitor ABT-530 and the NS3/4A ABT 530, which recently demonstrated 100 percent SVR12 rates with eight weeks of therapy in treatment-naïve genotype 3 without cirrhosis and with 12 weeks of therapy for treatment-naïve patients with cirrhosis.

The transition of therapy from an interferon-and-ribavirin-based regimen to DAA treatments has resulted in a marked improvement in eradicating genotype 1 infection. As a result, genotype 3 has emerged not only as the most virulent but also as the most difficult genotype to treat. The success of sofosbuvir in combination with agents such as daclatasvir has provided more avenues for treatment in patients with genotype 3 infections.

Though barriers in treatment still exist, including the high cost of therapy, the success of more recent trials holds promise that equal success to treating genotype 1 may be seen in the near future for genotype 3. In particular, the combination of pan-genotypic agents has a goal to shorten treatment courses while eliminating the need for ribavirin and providing high rates of SVR. Thus, while there is a pressing need to improve treatment options for genotype 3, new opportunities are on the horizon. ■

Nutrition and GI: STILL HAND IN HAND?

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Dr. Pickett-Blakely has no conflicts to disclose.

The connection between nutrition and gastroenterology should be intuitive given that gastroenterology involves the study of the organ system responsible for the digestion and absorption of nutrients. However, in my experience, nutrition is often an afterthought, being considered only after disease has negatively impacted an individual's nutritional status. In the early years of gastroenterology, Dr. William Beaumont reported his observations on gastric physiology and digestion after a series of experiments where he inserted food particles into the stomach via a gastrocutaneous fistula from a young fur trapper's musket wound. Beaumont's findings that gastric digestion depends on a combination of factors, including gastric acid, mechanical churning, temperature and what was later described as pepsin, were groundbreaking.[1] Though the early days of gastroenterology focused on alimentary physiology, primarily the digestive process, our current practice is quite different.

It is unclear where the connection between nutrition and gastroenterology diverged. Over time, the field of GI has evolved into subspecialties while concomitantly the focus in GI training programs has shifted to endoscopic proficiency and acute care.[2] GI fellowship programs devote minimal time, if any, to nutrition in their curricula.[3,4] I find that there is an unfortunate misconception that nutrition in clinical gastroenterology practice is solely restricted to nutrition support (e.g., parenteral and enteral nutrition). To the contrary, I agree with Mulder and colleagues who write: "There is a need for training in nutrition and nutrition-related issues because it lies at the core of gastrointestinal functioning and is very relevant to hepatogastroenterology practice."[5]

As a gastroenterologist, I find that nutrition is an integral component of my daily assessment of patients with gastrointestinal symptoms. A detailed history often reveals that symptoms may be provoked by ingesting certain foods and alleviated by avoiding certain foods. Similarly, weight loss is well recognized as an alarm symptom that signals discordance between energy intake and expenditure that may reflect organic disease of the alimentary tract. Furthermore, there are numerous examples of where diet and nutritional counseling are crucial to the management of the disease.

Celiac disease is an example of a disease for which diet is the cause of and treatment for the ailment. Similarly, nonalcoholic fatty liver disease (NAFLD), which is poised to overtake hepatitis C as the leading indication for liver transplant in the future, is another illustration of how nutrition is critical to gastroenterology practice. Given that the cornerstone of therapy for NAFLD remains behavioral modification via healthy diet and exercise, gastroenterologists should be equipped with basic skills to provide nutritional counseling to their patients. Lastly, consider bariatric surgery, which is performed commonly, and intentionally alters the structure and function of the GI tract for the purpose of weight loss. An understanding of the fundamentals of nutrient digestion is essential to proper long-term care in this patient population.

Nutrition and GI certainly do go hand in hand. It is essential that GI training programs reintroduce nutrition training into their curricula to ensure that the future of gastroenterology has a sound understanding of the fundamentals of nutrition and the mutual influence that nutrition and GI disease have on one another. Hopefully I have convinced the reader that gastroenterologists practice nutrition every day, and we all should embrace our inner nutritionist. ■

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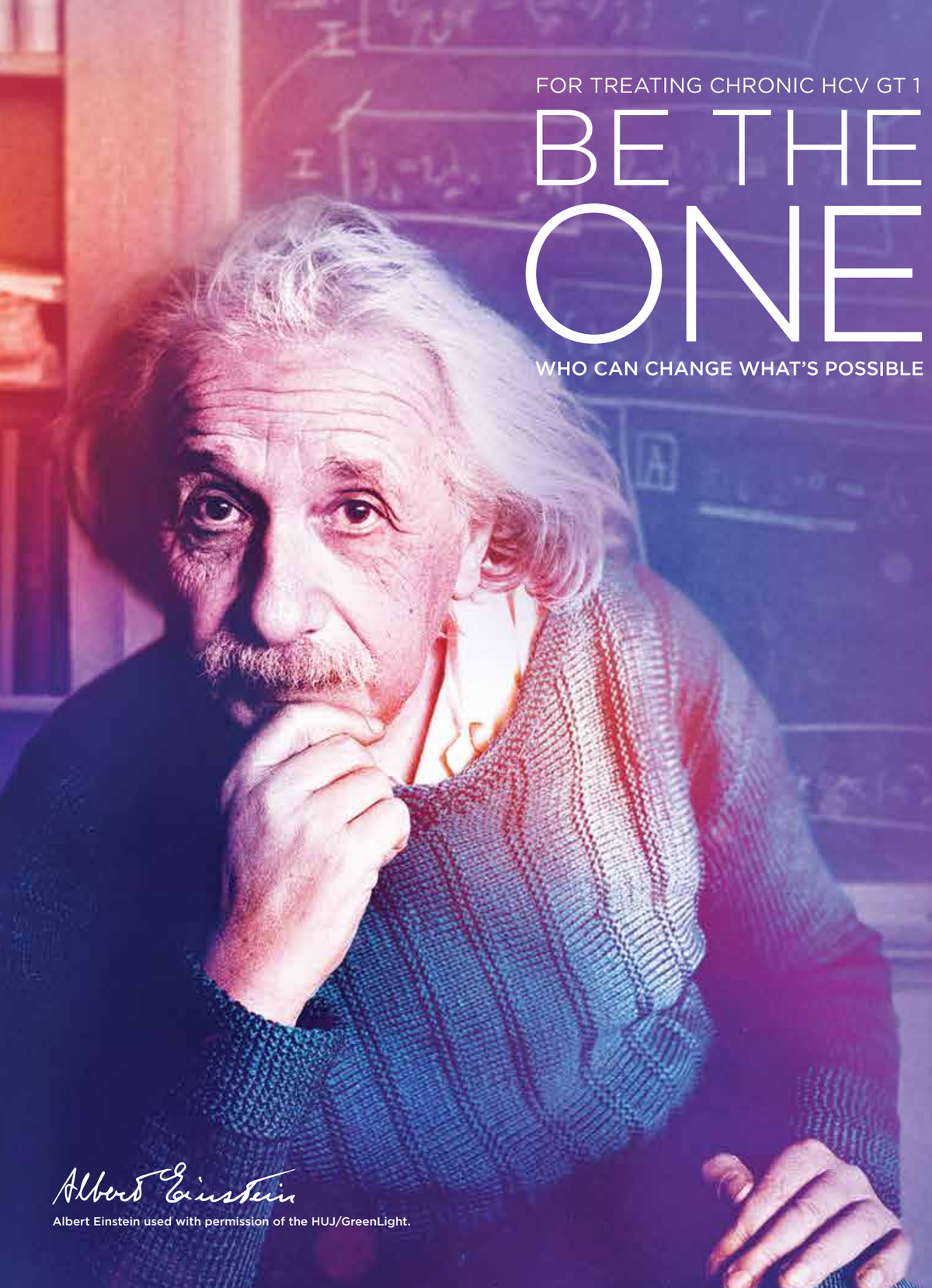


FOR TREATING CHRONIC HCV GT 1

BE THE ONE

WHO CAN CHANGE WHAT'S POSSIBLE

Albert Einstein

Albert Einstein used with permission of the HUJ/GreenLight.

HARVONI DELIVERED HIGH CURE (SVR) RATES IN SUBJECTS WITH HCV/HIV-1 CO-INFECTION[1,a]

96%

OVERALL CURE RATE IN GT 1 OR 4 HCV/HIV-1 CO-INFECTED SUBJECTS[1,a]

ION-4 (n=321/335)

- HARVONI delivered consistently high cure rates regardless of prior HCV treatment experience or cirrhosis status (94% in subjects with cirrhosis and 98% in treatment-experienced subjects with cirrhosis)[1]
- The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. See the Drug Interactions section of the HARVONI Prescribing Information for potentially significant drug interactions with HIV antiretrovirals[1]
- For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed on the next page[1]

[a]Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.[1] Achieving SVR is considered a virologic cure.[2]

Study Design[1]

ION-4: an open-label trial that included GT 1 and 4 treatment-naïve and treatment-experienced subjects (N=335) with HCV/HIV-1 co-infection with or without cirrhosis. Subjects received HARVONI for 12 weeks. Treatment-experienced subjects had failed prior treatment with Peg-IFN + RBV, Peg-IFN + RBV + an HCV protease inhibitor, or sofosbuvir + RBV. None of the 8 GT 4 subjects had cirrhosis. Subjects were on a stable HIV-1 antiretroviral therapy that included emtricitabine + tenofovir disoproxil fumarate, administered with efavirenz, rilpivirine, or raltegravir.

INDICATION

HARVONI is indicated with or without ribavirin for the treatment of patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

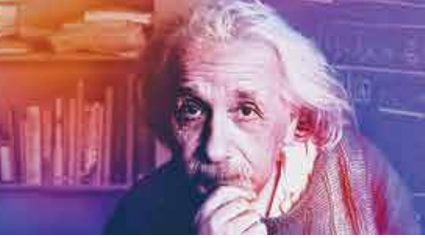
- If HARVONI is used in combination with ribavirin (RBV), all contraindications, warnings and precautions, in particular pregnancy avoidance, and adverse reactions to RBV also apply. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS

- **Risk of Serious Symptomatic Bradycardia When Coadministered with Amiodarone:** Amiodarone is not recommended for use with HARVONI due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.

Please see Brief Summary of full Prescribing Information on the following pages.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets



FOR TREATING CHRONIC HCV GT 1

BE THE ONE WHO CAN CHANGE WHAT'S POSSIBLE.
GO TO **HCP.HARVONI.COM/J2**

HARVONI IS THE ONLY SINGLE-TABLET REGIMEN FOR HCV GT 1 PATIENTS BUILT ON A SOFOSBUVIR BACKBONE[1]

1 TABLET ONCE A DAY
WITHOUT IFN OR RBV

Recommended treatment duration for HARVONI[1]

GT 1	8 weeks	Can be considered in TN patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL
	12 weeks	TN patients with or without cirrhosis TE patients without cirrhosis
	24 weeks	TE patients with cirrhosis[a]
GT 4, 5, 6	12 weeks	TN and TE patients with or without cirrhosis

- The dosing information listed here does not include patients with decompensated cirrhosis (Child-Pugh B or C) or liver transplant recipients
- For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed above. Refer to the Drug Interactions section of the HARVONI Prescribing Information for dosage recommendations for concomitant HIV-1 antiviral drugs[1]
- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]

[a]HARVONI + RBV for 12 weeks can be considered in TE GT 1 patients with cirrhosis who are eligible for RBV. The daily dosage of RBV is weight-based (1000 mg for patients <75 kg and 1200 mg for those ≥75 kg) administered orally in 2 divided doses with food. Refer to the RBV prescribing information.

Cirrhosis = compensated cirrhosis (Child-Pugh A), IFN = interferon, RBV = ribavirin, TE = treatment-experienced (patients who have failed a Peg-IFN alfa + RBV–based regimen with or without an HCV protease inhibitor), TN = treatment-naïve

HARVONI DELIVERED HIGH CURE (SVR) RATES IN A BROAD RANGE OF GT 1 SUBJECTS[1,b]

97%

OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS[1,3-5,b]
(n=1042/1079)

- Overall cure rates were 94%-99% across three HARVONI Phase 3 trials[1]
- The HARVONI clinical trial program enrolled the most challenging subjects, regardless of GT 1a or 1b subtype, prior experience with HCV therapy, or presence of cirrhosis[1]

[b]Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.[1] Achieving SVR is considered a virologic cure.[2]

Study Designs[1]
ION-3: a randomized, open-label trial in GT 1 treatment-naïve subjects (N=647) without cirrhosis. Subjects were randomized in a 1:1:1 ratio to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks. **ION-1:** a randomized, open-label trial in GT 1 treatment-naïve subjects (N=865) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks. **ION-2:** a randomized, open-label trial in GT 1 treatment-experienced subjects (N=440) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** Rifampin and St. John's wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.
- **Related Products Not Recommended:** HARVONI is not recommended for use with other products containing sofosbuvir.

HARVONI WAS SAFE WITH LOW RATES OF DISCONTINUATIONS AND ADVERSE EVENTS (AEs) ACROSS CLINICAL TRIALS[1,3-5]

≤1% **DISCONTINUATIONS DUE TO AEs[1]**

- Adverse reactions (all grades) reported in ≥5% of GT 1 subjects receiving 8, 12, or 24 weeks of treatment with HARVONI (in ION-3, ION-1, and ION-2): fatigue (13%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%)[1]
- No hematologic monitoring or dose adjustments are required with HARVONI[1]

MORE THAN 200,000 PATIENTS HAVE BEEN PRESCRIBED HARVONI IN THE US[6,c]

#1 **HARVONI IS THE #1 PRESCRIBED TREATMENT FOR HCV GT 1 IN THE US[7,8,d]**

[c]This information is derived from IMS NPA™, IMS NSP™, and IntegriChain® data; data reflect estimated patient starts for HARVONI from October 2014–November 2015.

[d]IMS Weekly NPA Market Dynamics™ from week-ending 11/14/14–1/1/16.

HELP YOUR PATIENTS GET STARTED ON HARVONI WITH SUPPORT PATH®

Support Path is a suite of resources that assists with benefits investigations and prior authorizations, and identifies potential financial assistance for patients, such as the HARVONI co-pay coupon program

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue, headache and asthenia.

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

HARVONI® (ledipasvir 90 mg and sofosbuvir 400 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated with or without ribavirin for the treatment of patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection.

CONTRAINDICATIONS
If HARVONI is administered with ribavirin (RBV), the contraindications to RBV also apply to this combination regimen. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS:

Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who will be coadministered HARVONI and patients taking HARVONI who need to start amiodarone, who have no other alternative, viable treatment options; and due to amiodarone's long half-life for patients discontinuing amiodarone just prior to starting HARVONI: Counsel patients about the risk of serious symptomatic bradycardia; and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Risk of Reduced Therapeutic Effect Due to Use With P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Risks Associated with RBV Combination Treatment
If HARVONI is administered with RBV, the warnings and precautions for RBV, in particular pregnancy avoidance, apply to this combination regimen. Refer to the RBV prescribing information.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir is not recommended.

ADVERSE REACTIONS:

Most common adverse reactions (incidence greater than or equal to 10%, all grades) were fatigue, headache and asthenia.

GT 1 Subjects with Compensated Liver Disease (With and Without Cirrhosis): The safety assessment of HARVONI was based on pooled data from three randomized, open-label Phase 3 clinical trials (ION-1, ION-3 and ION-2) in subjects who received HARVONI once for 8, 12 or 24 weeks. Adverse events led to permanent treatment discontinuation in 0%, less than 1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively. Adverse Reactions (adverse events assessed as causally related by the investigator; all grades; majority Grade 1) observed in at least 5% of subjects receiving HARVONI for 8, 12 or 24 weeks, respectively, were: fatigue (16%, 13%, 18%), headache (11%, 14%, 17%), nausea (6%, 7%, 9%), diarrhea (4%, 3%, 7%), and insomnia (3%, 5%, 6%). Direct comparison across trials should not be made due to differing trial designs.

GT 4, 5 or 6 Subjects with Compensated Liver Disease (With or Without Cirrhosis): The safety assessment of HARVONI was also based on pooled data from three open-label trials (Study 1119, ION-4 and ELECTRON-2) in 118 subjects who received HARVONI once daily for 12 weeks. The safety profile in these subjects was similar to that observed in subjects with chronic HCV GT 1 infection with compensated liver disease. The most common adverse reactions occurring in at least 10% of subjects were asthenia (18%), headache (14%) and fatigue (10%).

GT 1 Treatment-Experienced Subjects with Cirrhosis (SIRIUS): The safety assessment of HARVONI with or without ribavirin (RBV) was based on a randomized, double-blind and placebo-controlled trial. Subjects were randomized to receive HARVONI once daily for 24 weeks without RBV or 12 weeks of placebo followed by 12 weeks of HARVONI + RBV. Adverse reactions (all grades; majority Grade 1 or 2) observed in at least 5% greater frequency reported in subjects receiving HARVONI for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively, were: asthenia (31% or 36% vs 23%); headache (29% or 13% vs 16%); fatigue (18% or 4% vs 1%); cough (5% or 11% vs 1%); myalgia (9% or 4% vs 0%); dyspnea (3% or 9% vs 1%); irritability (8% or 7% vs 1%); and dizziness (5% or 1% vs 0%).

Liver Transplant Recipients and/or Subjects with Decompensated Cirrhosis: The safety assessment of HARVONI + RBV in liver transplant recipients and/or those who had decompensated liver disease was based on pooled data from two Phase 2 open-label clinical trials including 336 subjects who received HARVONI + RBV for 12 weeks. Subjects with Child-Pugh-Turcotte (CPT) scores greater than 12 were excluded from the trials. The adverse events observed were consistent with the expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known safety profile of HARVONI and/or ribavirin. Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 38% and 13% of subjects treated with HARVONI + RBV for 12 weeks, respectively. Ribavirin was permanently discontinued in 11% of subjects treated with HARVONI + RBV for 12 weeks.

Liver Transplant Recipients with Compensated Liver Disease: Among the 174 liver transplant recipients with compensated liver disease who received HARVONI + RBV for 12 weeks, 2 (1%) subjects permanently discontinued HARVONI due to an adverse event. *Subjects with Decompensated Liver Disease:* Among the 162 subjects with decompensated liver disease (pre- or post-transplant) who received HARVONI + RBV for 12 weeks, 7 (4%) subjects died, 4 (2%) subjects underwent liver transplantation, and 1 subject (<1%) underwent liver transplantation and died during treatment or within 30 days after discontinuation of treatment. Because these events occurred in patients with advanced liver disease who are at risk of progression of liver disease including liver failure and death, it is not possible to reliably assess the contribution of drug effect to outcomes. A total of 4 (2%) subjects permanently discontinued HARVONI due to an adverse event.

GT 1 or 4 Subjects with HCV/HIV-1 Co-infection (ION-4): The safety assessment of HARVONI was based on an open-label clinical trial in 335 subjects who were on stable antiretroviral therapy. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. The most common adverse reactions occurring in at least 10% of subjects were headache (20%) and fatigue (17%).

Less Common Adverse Reactions Reported in Clinical Trials (less than 5% of subjects receiving HARVONI in any one trial): These events have been included because of their seriousness or assessment of potential causal relationship. *Psychiatric disorders*: depression (including in subjects with pre-existing history of psychiatric illness). Depression, particularly in subjects with pre-existing history of psychiatric illness, occurred in subjects receiving sofosbuvir containing regimens. Suicidal ideation and suicide have occurred in less than 1% of subjects treated with sofosbuvir in combination with ribavirin or pegylated interferon/ribavirin in other clinical trials.

Laboratory Abnormalities: *Bilirubin Elevations:* Elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 3%, 11% and 3% of subjects with compensated cirrhosis treated with placebo, HARVONI + ribavirin for 12 weeks and HARVONI for 24 weeks, respectively. *Lipase Elevations:* Transient, asymptomatic elevations of greater than 3x ULN were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 1%, 3% and 9% of subjects with compensated cirrhosis treated with placebo, HARVONI + ribavirin for 12 weeks and HARVONI for 24 weeks, respectively. *Creatine Kinase:* was not assessed in Phase 3 trials ION-1, ION-3 or ION-2 of HARVONI but was assessed in the ION-4 trial. Isolated, asymptomatic creatine kinase elevations of greater than or equal to 10xULN was observed in 1% of subjects treated with HARVONI for 12 weeks in ION-4 and has also been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

Brief Summary (cont.)

Postmarketing Experience: Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Cardiac Disorders:* Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI during post approval use of HARVONI. *Skin and Subcutaneous Tissue Disorders:* Skin rashes, sometimes with blisters or angioedema-like swelling

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. This list includes potentially significant interactions but is not all inclusive.

Alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:

Acid Reducing Agents: Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration. *Antacids:* Separate HARVONI and antacid administration by 4 hours. *H_2-receptor antagonists*: Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI. *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.

Antiarrhythmics (amiodarone; digoxin) *Amiodarone:* Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin:* Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.

Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine): Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

Antimycobacterials (rifabutin; rifampin; rifapentine): Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

HIV Antiretrovirals

Regimens containing tenofovir disoproxil fumarate (DF) without a HIV protease inhibitor/ritonavir or cobicistat: Due to increased tenofovir concentrations, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir or cobicistat (e.g., atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF, darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF, lopinavir/ritonavir + emtricitabine/tenofovir DF): The safety of increased tenofovir concentrations has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Elvitegravir/cobicistat/emtricitabine/tenofovir DF: The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.

Tipranavir/ritonavir: Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

HCV Products (simeprevir): Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.

Herbal Supplements (St. John's wort): Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.

HMG-CoA Reductase Inhibitors (rosuvastatin): Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions and use with certain HIV antiretroviral regimens; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Consider the benefits and risks of HARVONI when prescribing to a pregnant woman. If HARVONI is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information.

Lactation: It is not known if HARVONI and its metabolites are secreted in human breast milk. Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk without clear effect on nursing pups. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the breastfed infant from HARVONI or from the underlying maternal condition. If HARVONI is administered with RBV, the lactation information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 225 subjects aged 65 and over (9% of total number of subjects in the clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C).

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NEW OPTIONS ON THE HORIZON FOR IBS-D

RON SCHEY, MD, FACG

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Associate Director of Neurogastroenterology and Esophageal Disorders Program
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Dr. Schey has no conflicts to disclose.

A 21-year-old female college junior entered my office and sat down. I asked her how she was doing and she replied, "My IBS is a 24/7 living nightmare. I have to monitor everything I eat, where the nearest bathroom is, how long the car or bus ride will be, and of course avoid flying at any cost." After a short pause she continued, "If that's not enough, my classmates and professors always make sure the first row seat next to the exit door is saved for me, and I am constantly being asked about the location of toilets all over the whole campus … oh you really don't want to know what happens during my exams." At this point, she was tearful and I reached out and handed her a tissue.

The prevalence of irritable bowel syndrome (IBS) is about 15 percent of the general global population. The main symptoms include abdominal pain or discomfort (relieved by defecation) and disordered bowel function. Currently, IBS is diagnosed using Rome criteria (Rome IV was released in May 2016) and subclassified according to predominant stool patterns as either constipation, diarrhea, mixed type or unclassified. About 35 to 40 percent of patients with IBS have diarrhea-predominant bowel symptoms. IBS-D is associated with impairment in health-related quality of life, places a considerable financial burden on society because of reduced work productivity and increases the use of health-related resources.[1,2]

The postulated pathophysiological factors of IBS-D include: dietary effects on gut permeability and microbiota, alterations in central nervous system innervation and processing of GI-tract stimulation with an increased number of colonic mast cells (leading to reduced pain thresholds throughout the GI system) and disruptions in serotonin signaling with a greater number of serotonin-positive enterochromaffin cells in the crypt epithelium, leading to increased number of colonic contractions, accelerated transit and alterations in small bowel motor function. In addition, one quarter of patients meeting accepted criteria for IBS-D have bile acid malabsorption.[3-5]

When we discuss diagnostic testing for IBS-D it is important to emphasize that extensive diagnostic testing in the absence of alarm symptoms is unnecessary and should be avoided; hence, stick to Rome criteria and you will be OK.

> In 2015, FDA approved two drugs that significantly broaden the potential treatment available for patients with IBS-D.

Until recently, the traditional treatment for IBS-D included dietary and lifestyle modifications (low FODMAP, gluten-free, low-carb diets), probiotics (B. infantis), antidiarrheal agents (loperamide), and alosetron (serotonin 5HT3 receptor antagonist), which is currently available only for females under a risk management program. Antispasmodics (dicyclomine and hyoscyamine) and peppermint oil relieve muscle contractions without really affecting the diarrhea and are worth a try as an addition to treatment but not as a sole treatment. Colesevelam (bile acid sequestrant) increases stool consistency and decreases number of bowel movements in IBS-D patients with bile acid malabsorption. Additionally, the role of fecal transplants in *Clostridium difficile* treatment is currently promising, yet its role in IBS-D is still investigational and thus far not part of our regimen.

In 2015, FDA approved two drugs (rifaximin and eluxadoline) that significantly broaden the potential treatment available for patients with IBS-D, thus significantly adding to the current therapeutic options for IBS-D patients.

Rifaximin (nonsystemic antibiotic) 550 mg given three times daily for two weeks significantly improved symptoms at two and four weeks post treatment (probably hanging in there almost up to 10 weeks) in the TARGET 1 and 2 studies. TARGET 3 verified that it is efficacious and safe (slim chance of *Clostridium difficile*) to re-treat at least two more times (in 10 week intervals).[6]

Eluxadoline, a mixed mu opioid agonist and delta opioid antagonist (75,100mg twice-daily), significantly improved stool consistency, urgency and frequency for up to six months compared to placebo in a multicenter study. It is important to emphasize that it should not be given to patients with a history of bile duct obstruction, sphincter of Oddi dysfunction, pancreatitis, alcoholism or alcohol abuse.[7]

I believe that traditional therapies continue to play a role in treatment of IBS-D. Additionally, with our greater understanding of the mechanisms in IBS-D, recent new drugs add to our available treatment and help complement other therapies to improve symptoms and quality of life in patients with IBS-D.

In other chronic diseases, we are beginning to see promising results in studies that look at text messaging as a means to provide patients with reminders to take their medications. However, studies are needed to determine if such modalities have a role in improving the care of patients with IBS-D. A key tenet of quality improvement is to measure your personal or practice performance. ImproveCareNow is a consortium of multiple pediatric GI practices that share data on the health of their patients. The organization has increased remission rates in pediatric IBD patients through collaborative data-sharing networks across patients, hospitals and providers while lowering costs, and provides a helpful model for other practices interested in forming similar consortiums

Cornerstones Health has developed a valuable health maintenance checklist at www.cornerstoneshealth.org/checklist that allows both providers and patients to keep track of key health maintenance issues such as vaccines, bone health and cancer prevention online. And with the advent of electronic health records, gastroenterologists can embed health-maintenance checklists directly into patients' charts. In our practice, we have developed an IBD outpatient form in our electronic health record software, Epic, which populates the encounter with vaccination dates, important lab data and hepatitis A and B antibody status, allowing easy access to these data. The Crohn's and Colitis Foundation of America is also developing an Epic IBD encounter form that will be available to sites using their software.

Despite many of these advancements and new techniques that we have listed above, more research is still needed to see if implementation of such technologies, screenings and informational methods can improve adherences to measures detailed by AGA, and ultimately improve the care we provide to our IBS patients. ■

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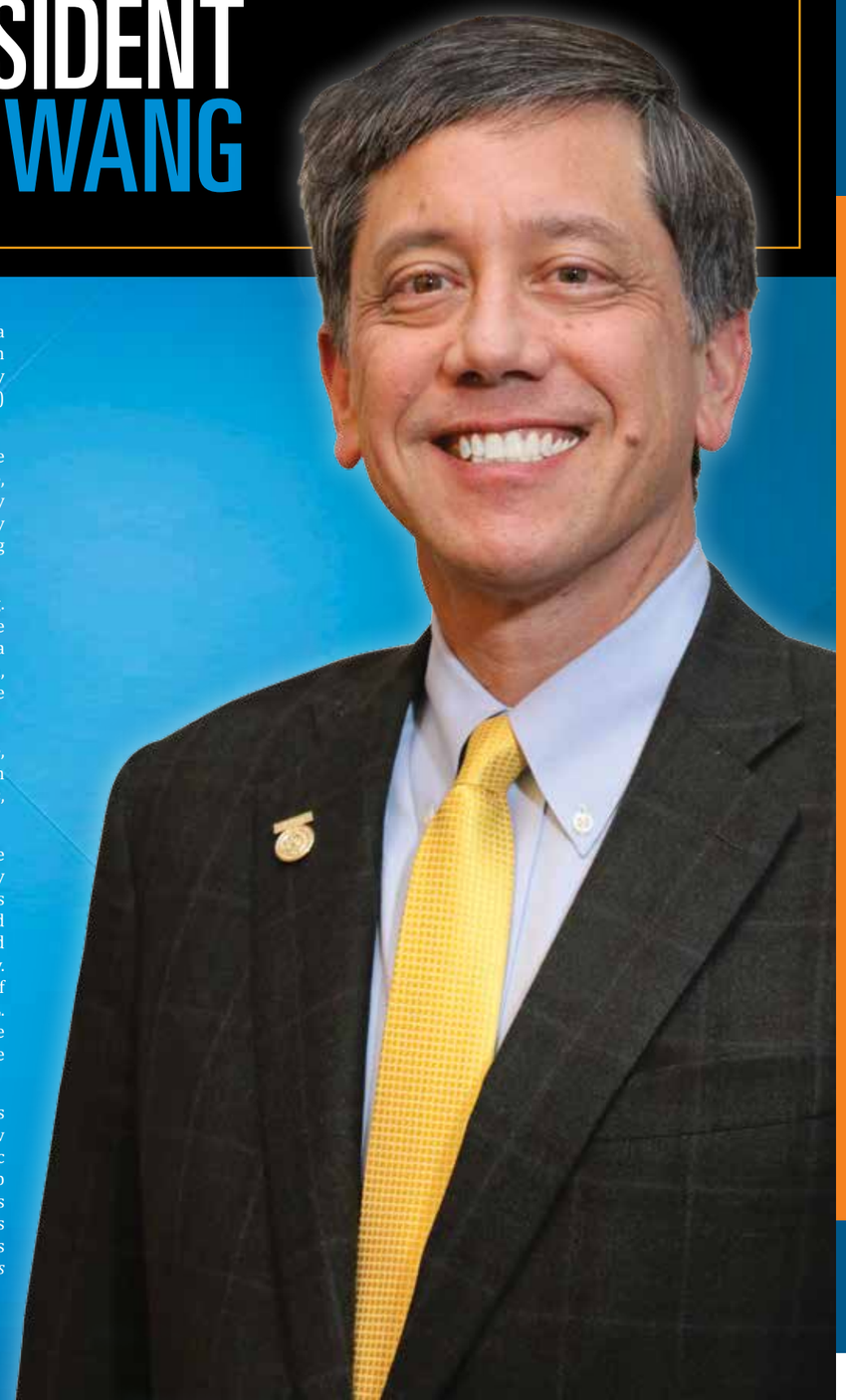
INSIDE AGA

AGA WELCOMES NEW PRESIDENT TIMOTHY WANG



Timothy Wang, MD, AGAF, of Columbia University began his term as the 111th president of AGA Institute immediately after Digestive Disease Week® (DDW) 2016 this May.

Dr. Wang has been an active AGA member since 1986, serving on the AGA By-Laws Committee, AGA Public Policy Committee and most recently as chair of the AGA Institute Research Policy Committee and member of the AGA Governing Board as president-elect.

"Health care and gastroenterology are changing. I'm thrilled to lead AGA and represent the needs of the GI community as we navigate a rapidly evolving system shaped by innovation, regulation, scarce research funding and practice in a consumer-driven setting," said Dr. Wang.

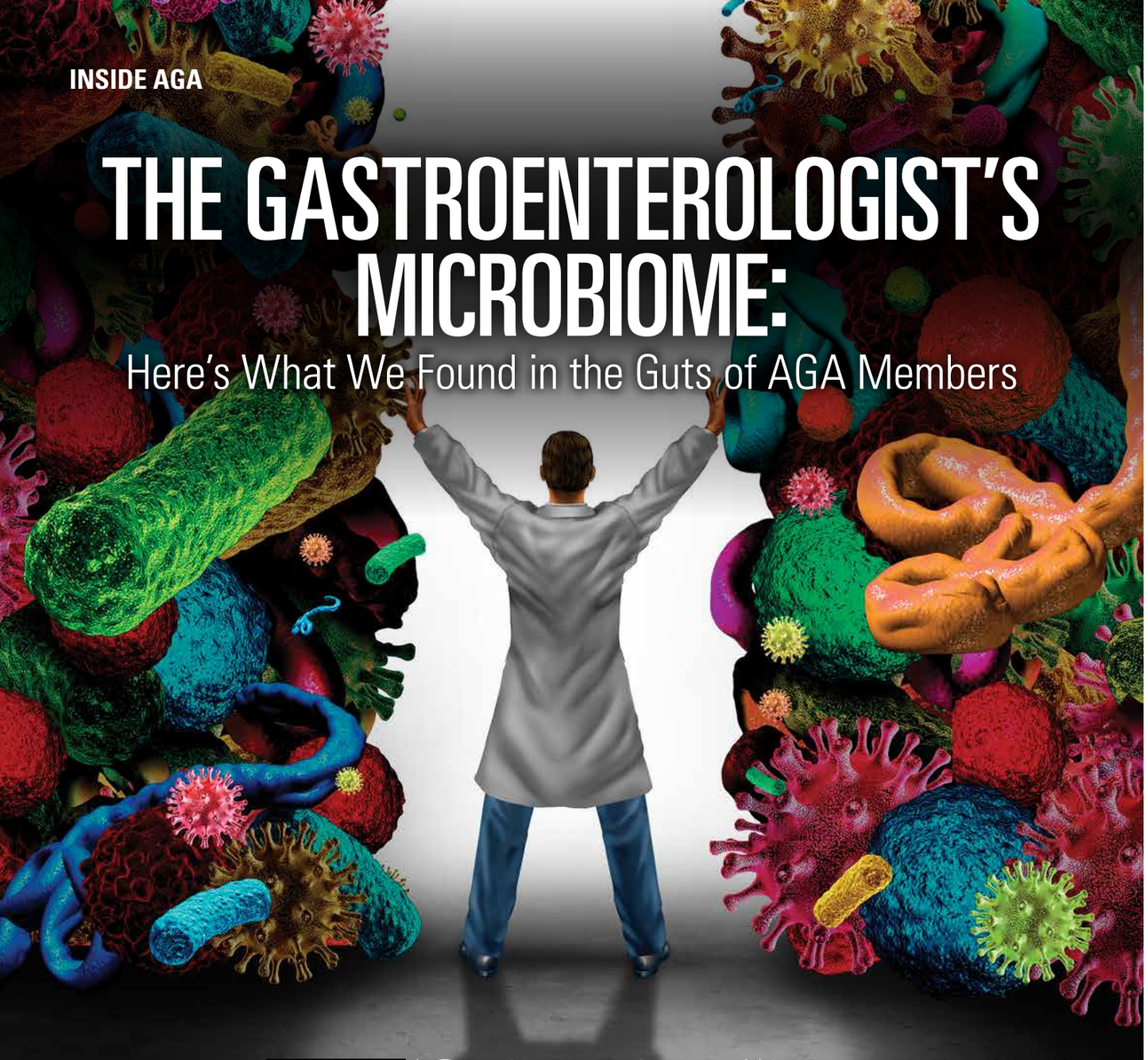
Dr. Wang received his BA from Williams College, Williamstown, MA, and his medical degree from Columbia College of Physicians and Surgeons, New York, NY.

He completed his residency in internal medicine at Barnes Hospital, Washington University School of Medicine, in St. Louis, MO, and his research fellowship in medicine at Harvard Medical School, Boston, MA. He is board certified in internal medicine and gastroenterology. Dr. Wang has served as chief of the division of digestive and liver diseases and the Dorothy L. and Daniel H. Silberberg professor of medicine at Columbia University Medical Center since 2005.

Dr. Wang has won numerous awards for his work, including the AGA senior research fellow award, AGA Robert & Sally Funderburg Gastric Cancer Award and Steven Krane Lectureship for Outstanding Young Investigator. He has served as associate editor for AGA's publications *Gastroenterology and GI & Hepatology News*, as well as editor-in-chief for *Therapeutic Advances in Gastroenterology*.

THE GASTROENTEROLOGIST'S MICROBIOME:

Here's What We Found in the Guts of AGA Members



ROB KNIGHT, PHD

Rob Knight, PhD, Principal Investigator, Knight Lab; Professor, Department of Pediatrics, University of California, San Diego

Co-founder, American Gut

Member of the AGA Center for Gut Microbiome Research and Education strategic advisory board.

Dr. Knight has no conflicts to disclose.

Since the Human Microbiome Project[1] launched in 2008, we've learned from hundreds of studies that the microbiome — all of the bacteria, archaea, viruses and fungi that live on us and in us — is associated with human disease. Inflammatory bowel disease (IBD) and obesity are some examples of interest to gastroenterologists where the microbiome clearly has an impact. As a result, there is enthusiasm for leveraging the therapeutic potential of the microbiota. However, we still have much to learn before the microbiome becomes a treatment option for clinicians. Statistical power is key, and therefore, so are large sample sizes.

The American Gut Project[2], the country's largest open source citizen science project, is making great strides toward this goal. As of May 2016, the project has processed over 9,000 samples from over 7,000 individuals. To continue growing and diversifying the project, American Gut has reached out to various groups along the health spectrum such as patients, athletes, and now physicians thanks to a collaboration with the AGA and its Center for Gut Microbiome Research and Education3.

At Digestive Disease Week® (DDW) 2016, the center hosted a one-of-a-kind session titled Active Learning Session on the Gut Microbiome: Fundamental Principles in Theory and Practice. AGA member volunteers submitted stool samples to American Gut for analysis in advance of the session. In addition to the individual results that participants would normally receive, American Gut also performed a special cohort analysis to see if the guts of gastroenterologists differ from those of our larger volunteer pool.

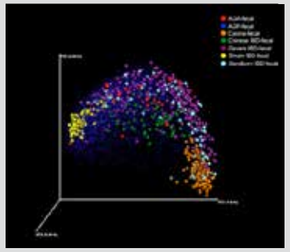


Figure 1. PCoA plot illustrating the seven datasets analyzed in the current meta-analysis. Each dot represents a single sample and are colored by study. Red = AGA volunteers ("AGA-fecal"); dark blue = American Gut ("AGP-fecal"); orange = canine IBD ("Canine-fecal"); green = Chinese IBD ("Chinese IBD-fecal"); purple = adolescent IBD ("Gevers IBD-fecal"); yellow = individual Crohn's patient ("Smarr IBD-fecal"); and U.S. IBD (light blue, "Sandborn IBD-fecal").

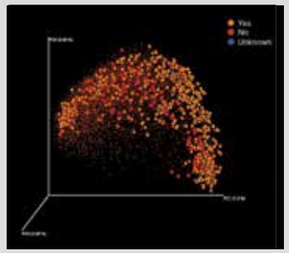


Figure 2. PCoA plot with samples colored according to IBD status. Orange = IBD (yes), red = healthy (no), blue = IBD status unknown.

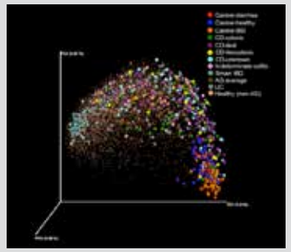


Figure 3. PCoA plot illustrating samples colored by disease subtype. Red = canines with diarrhea; blue = healthy canines; orange = canines with IBD; green = colonic Crohn's disease; purple = ileal Crohn's disease; light blue = ileocolonic Crohn's disease; pink = indeterminate colitis; teal = longitudinal samples from individual Crohn's patient (Smarr); brown = American Gut average; gray = ulcerative colitis; coral = healthy patients from IBD datasets (excluding American Gut).

The American Gut dataset, including AGA volunteer samples, was compared with four other human datasets: a U.S. IBD cohort including both Crohn's and ulcerative colitis patients[4], an adolescent Crohn's cohort[5], a Chinese Crohn's disease cohort[6], and a single individual diagnosed with Crohn's disease with longitudinal samples spanning months[7]. We also included a canine IBD dataset to assess species-specific differences and similarities. Leveraging Qiita, an open-source microbiome data storage and analysis resource developed in our lab[8], we conducted a meta-analysis of all of these studies together.

Figure 1 shows a principal coordinates analysis (PCoA) plot of the meta-analysis. Each dot on the plot represents a single sample. The closer together two samples are on the plot, the more similar the microbial communities represented by those dots; the further apart two samples are, the more dissimilar the microbial communities.

The first thing you may notice is that the AGA samples (red) are widely distributed, as are the American Gut samples (dark blue, small dots). Most AGA samples came from individuals that do not suffer from IBD. Notably, the longitudinal samples from the individual Crohn's patient (yellow) clustered separately from the U.S. IBD cohort (light blue), the adolescent Crohn's cohort (purple), and the Chinese Crohn's cohort (green).

The Chinese cohort also forms an obvious cluster; this is likely due to differences in diet between individuals in the Chinese cohort and the other cohorts, which were largely North American patients with "Western" diets. Interestingly, some samples from the U.S. and adolescent IBD cohorts clustered with the canine samples, indicating that microbially these samples were more similar to dog samples than to the other human samples in the meta-analysis.

To learn more about the gut microbiome, visit the AGA Center for Gut Microbiome Research & Education at **www.gastro.org/microbiome.**

The datasets can also be visualized differently to look for patterns of clustering across studies. Here, additional visualization by IBD diagnosis (**Figure 2**) and by IBD subtype (**Figure 3**) are shown. Neither revealed obvious clustering patterns, indicating that overall microbiome composition is not notably associated with specific IBD subtypes among the seven studies in this meta-analysis.

However, this may be due to the large size of the American Gut cohort (over 6,000 fecal samples) compared to the other studies. Additionally, any specific associations by IBD subtype could be present at levels (e.g., at the individual species or strain level) not detectable with the methodology used in this analysis. It is important to note that American Gut participants self-report diseases and their reported diagnoses are not independently verified. This underscores the potential benefits of collecting samples from well-characterized diseased cohorts to fully piece together the connection between the microbiome and IBD.

This is just a glimpse into the findings from our collaboration with AGA and additional insights are available on http://www.gastro.org/about/initiatives/AGA-American_Gut_Handout_DDW_2016.pdf.[9] A recording of the center's DDW 2016 session is also available to view at DDW On Demand. At American Gut, we look forward to continued analyses and building connections between the human microbiome and health. We will continue to share our knowledge and findings with AGA members through the AGA Center for Gut Microbiome Research and Education. ■

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ROLE AND TIMING OF ERCP IN SUSPECTED CHOLEDOCHOLITHIASIS

B. JOSEPH ELMUNZER, MD

Division of Gastroenterology and Hepatology
Medical University of South Carolina

Dr. Elmunzer has no conflicts to disclose.

When evaluating a patient with suspected choledocholithiasis, the fundamental question is whether or not to recommend an endoscopic retrograde cholangiopancreatography (ERCP). Given its risks, and with the more widespread availability of endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP), ERCP has become (or at least should be) a nearly exclusively therapeutic tool. In order to restrict ERCP to patients with the highest probability of ongoing choledocholithiasis — in whom the risk-benefit ratio is most favorable — accurate and reproducible risk stratification strategies are necessary.

The most widely used strategy is an algorithm proposed by ASGE that selects patients for ERCP versus less invasive tests (EUS, MRCP or intraoperative cholangiography [IOC]) based upon readily available clinical, laboratory and radiographic predictors.[1] We and others have conducted six validation studies to date (comprising 2,052 patients), which demonstrate that the accuracy of the ASGE guidelines is in the range of 55 to 70 percent, potentially exposing a sizeable fraction of patients to unnecessary ERCP.[2–7] However, the acceptable rate of "negative" ERCP for suspected choledocholithiasis is a value judgment based on multiple factors, including local ERCP expertise and the availability, cost and performance characteristics of alternative diagnostic modalities. Indeed, while we concluded from these data that the guidelines are not adequately sensitive and specific to drive clinical management, the authors of a recent prospective validation study concluded that the 70 percent accuracy they observed in their cohort justifies the routine use of the guidelines in clinical practice.[5] Similarly, surveyed practitioners caring for patients with biliary disease considered 2.5 (95 percent CI, 2.2–2.83) negative ERCPs per every 10 procedures an acceptable rate.[8]

Given this subjectivity and the absence of a highly accurate and widely accepted risk-stratification strategy, at our institution we generally begin the conversation with the ASGE guidelines but then adjust the plan in response to factors that are not accounted for in existing algorithms, having a low threshold to pivot toward less invasive tests in patients deemed to be at high probability for choledocholithiasis by the ASGE guidelines. For example, we may opt for less invasive testing in a high-probability patient with improving abdominal pain and an increased appetite on the day after admission. When this pivot occurs in a high-probability patient, we generally favor EUS over MRCP because it is more sensitive for small stones and does not delay care when performed in an ERCP-capable endoscopy suite. In patients at intermediate probability, we select MRCP, EUS or IOC based on test availability and the expertise of the involved surgeon.

However, given the possible disadvantages of overusing EUS and MRCP, but acknowledging the morbidity and costs associated with ERCP-related adverse events, it remains reasonable to strive toward a highly accurate stratification system that eliminates most (greater than 90 percent) diagnostic ERCPs while remaining cost and resource neutral. To this end, several alternative strategies have been proposed:

1) A pilot randomized trial comparing an EUS-guided strategy to up-front ERCP in all comers with suspected choledocholithiasis (but no concern for cholangitis) revealed that initial EUS reduced procedure time and adverse events without affecting stone-related outcomes.[9] On this basis, and recognizing the limitations of existing guidelines, some experts have adopted a strategy of routine EUS at the time of possible ERCP in all patients with suspected choledocholithiasis but no evidence of ascending cholangitis. Additional research on the EUS-first strategy is warranted since endosonographic evaluation of the biliary tree is safe, accurate and can be accomplished quickly at the time of possible ERCP.

2) Several alternative scoring systems based on basic biochemical testing and bile duct size have demonstrated better performance characteristics than existing guidelines, albeit in small patient cohorts. One simple scoring strategy aims to risk-stratify patients to undergo cholecystectomy alone (score equals 0), IOC (score equals 1 or 2), MRCP (score equals three or 4) or ERCP (score equals 5). This scoring is based on initial biochemical laboratory tests (gamma glutamyl transferase greater than or equal to 350 U/L, alkaline phosphatase greater than or equal to 250 U/L, total bilirubin greater than or equal to 3 mg/dL, and direct bilirubin greater than or equal to 2 mg/dL) and common bile duct size (greater than or equal to 9 mm) on transabdominal ultrasound. This strategy eliminated negative ERCPs entirely in a small number of patients with suspected gallstone pancreatitis.[10] Such strategies certainly merit validation in larger, diverse patient populations.

3) Advanced predictive modeling techniques may also hold promise. A recently developed artificial neural network model predicted choledocholithiasis with an area under the receiver operating characteristic curve of 0.88 (95 percent CI, 0.831–0.938).[11] Unfortunately, machine-learning algorithms did not substantially outperform the ASGE algorithm in our cohort of approximately 700 patients from two academic institutions.[15]

4) We hypothesized that the trend in liver function tests over time is clinically informative, with decreasing values suggesting spontaneous stone passage and prompting less invasive initial intervention. However, we conducted two studies in different geographic and socioeconomic populations, which demonstrated that the evolution of liver chemistries over time does not predict persistent choledocholithiasis.[3,6]

When considering ERCP for suspected choledocholithiasis, three important caveats are worth mentioning. First, in patients at intermediate risk who are not cholecystectomy candidates, upfront ERCP for biliary sphincterotomy to reduce the risk of recurrence is reasonable, and confirmatory testing is generally not needed.[12] Second, in the context of suspected choledocholithiasis, the presence of a prior biliary sphincterotomy is likely highly protective against post-ERCP pancreatitis because it facilitates cannulation and reduces the risk of pancreatic injury by separating the biliary and pancreatic orifices. In such cases, I have a lower threshold to proceed with ERCP. Third, in patients undergoing cholecystectomy who require ERCP, most surgeons prefer that stones be cleared pre operatively, although intra-operative and post-operative ERCP have been shown to be safe and equally effective.[13,14]

In conclusion, the fundamental question of when to perform ERCP for suspected choledocholithiasis remains unanswered, although several intriguing lines of research may provide clarity. In the interim, a thoughtful case-by-case strategy founded on existing evidence, but sensitive to the principle of minimizing unnecessary risk, will serve our patients well. ■

It remains reasonable to strive toward a highly accurate stratification system that eliminates most (greater than 90 percent) diagnostic ERCPs while remaining cost and resource neutral.

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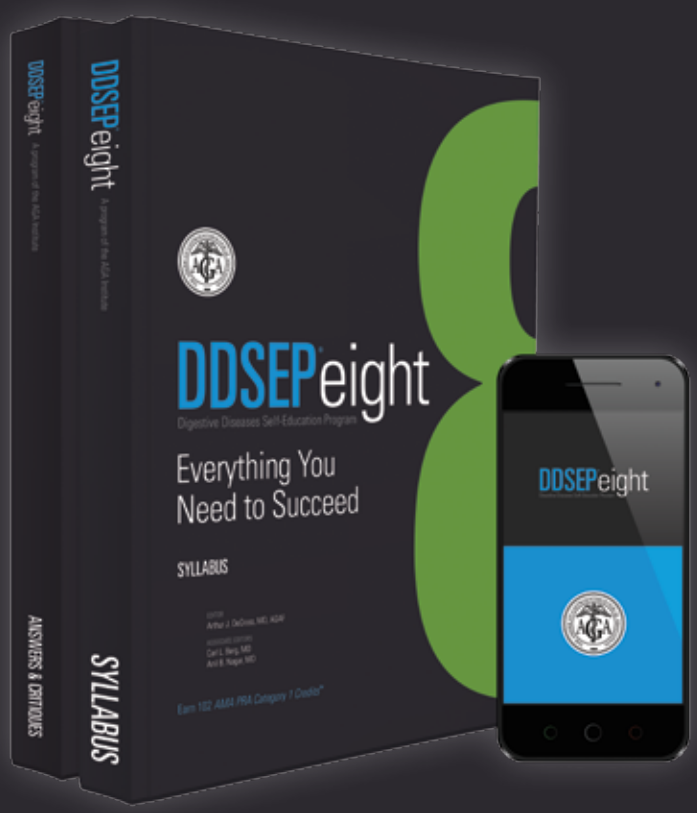

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