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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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

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We welcome member feedback on all of the perspectives presented in this issue. Send your letters and comments to communications@gastro.org and include “AGA Perspectives” in the subject line.

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Estimates are that only 20% of the $1.3 billion being paid for anesthesiologist-directed sedation was earmarked for high-risk patients. 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? What is best for the patient? Does anesthesiologist-directed sedation lead to improvements in the outcomes of ambulatory endoscopic procedures? A nesthesiologist-directed sedation for ambulatory endoscopic procedures has enjoyed an unparalleled and unbridled 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 the $1.3 billion being paid for anesthesiologist-directed sedation, only $200 million was earmarked for high-risk patients. 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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**View from an Anesthesiologist**

**Jeff Mandel, MD, MS**
Assistant Professor of Anesthesiology and Critical Care, Attending Anesthesiologist, the Hospital of the University of Pennsylvania

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 you.

**View from a Gastroenterologist**

**John J. Vargo, MD, MPH, AGAF**
Chair, Department of Gastroenterology and Hepatology, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH

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**Anesthesiologist - Cont. on page 6**

**Gastroenterologist - Cont. on page 7**
ANESTHESIOLOGIST - CONT. FROM PAGE 5

Doing the math

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.

Data from my research group suggests a range of effect site levels required for endoscopy varies by a factor of four. 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. 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

GASTROENTEROLOGIST - CONT. FROM PAGE 5

For colonoscopy, when compared to endoscopist-directed sedation, there was no safety benefit for anesthesiologist-directed sedation.
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 have 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 pharmacokineticocontrol of propofol that simplify the task of the anesthesiologist, permitting a different staffing model, perhaps 1:3.6 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 payers, 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.

**REFERENCES**


be 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 but 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.

This scientific version of the reality TV show is simplified by some studies linking proton pump inhibitors (PPIs) to a variety of diseases. PPIs have been associated with GI infections (such as Clostridium difficile), pneumonia, bone fractures, pernicious anemia, interactions with clopidogrel and heart disease. To this we can now add chronic renal disease and dementia.1 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.2 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 pursue 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.3 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.4 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 the OR equals 1.76 (95 percent CI = 1.15 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.6,7 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.

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. 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.”8

**References**

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, FUSSION, 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 genotype 3.

The ELECTRON-2 trial investigated the use of the NSSA 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 SVR 12 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?

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 described as pepsin, were groundbreaking. 1 churning, temperature and what was later of factors, including gastric acid, mechanical that gastric digestion depends on a combination 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 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 nutritionists. 

REFERENCES
2. Dubois A, Johnson LF. “The AGA Clinical Guidelines App is a product of the AGA Institute.”
3. Scolapio JS, Buchman AL, Floch M. “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 nutritionists. 

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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.

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

OVERALL CURE RATE IN GT 1 OR 4 HCV/HIV-1 CO-INFECTED SUBJECTS

ION-4 (n=321/335)

96%

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

• 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

“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. Achieving SVR is considered a virologic cure.”

Study Design

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.

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

Albert Einstein used with permission of the HUJ/GreenLight.
HARVONI IS THE ONLY SINGLE-TABLET REGIMEN FOR HCV GT 1 PATIENTS BUILT ON A SOFOSBUVIR BACKBONE

HARVONI WAS SAFE WITH LOW RATES OF DISCONTINUATIONS AND ADVERSE EVENTS (AEs) ACROSS CLINICAL TRIALS

- 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%).

- No hematologic monitoring or dose adjustments are required with HARVONI.

MORE THAN 200,000 PATIENTS HAVE BEEN PRESCRIBED HARVONI IN THE US

HELP YOUR PATIENTS GET STARTED ON HARVONI WITH SUPPORT PATH

IMPORTANCE 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 tizanidine due to the potential for the drug interactions listed below. Consult the full Prescribing Information for information on potentially significant drug interactions, including clinical comments.

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

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

- Overall cure rates were 94%-99% across three HARVONI Phase 3 trials.
- 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.

IMPORTANT SAFETY INFORMATION (continued)

- Risk of Reduced Therapeutic Effect of HARVONI Due to Pgp 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.

- 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.

- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir.

- 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-naive.

- Unwarranted administration of RBV is not recommended in TE GT 1 patients with cirrhosis 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.

- Interactions with the HBV/HCV protease inhibitors boceprevir and telaprevir are not recommended with HARVONI as they may significantly decrease ledipasvir and sofosbuvir concentration.
Among the 162 subjects with liver disease. The most common adverse reactions occurring in at least 5% greater frequency reported in subjects receiving HARVONI + RBV for 24 weeks or HARVONI + RBV + PEG for 24 weeks compared to placebo for 12 weeks, respectively, were: headache (20% or 13% vs 16%), fatigue (18% or 4% vs 14%), cough (5% or 11% or 1%), myalgia (5% or 4% vs 0%), diarrhea (5% or 9% or 1%), asthenia (3% or 0% vs 8%), neutropenia (2% or 7% vs 0%), and nasopharyngitis (1% or 0% vs 3%).

Liver Transplant Recipients and/or Subjects with Decompensated Cirrhosis: Among 174 liver transplant recipients (109 with decompensated cirrhosis) and/or subjects (20 with decompensated cirrhosis) who were co-administered HARVONI, 336 subjects who received HARVONI + RBV for 12 weeks. Subjects with Child-Pugh-Turcotte (CPT) score greater than 12 were excluded from the treatment. Liver biopsy samples were consistent with the expected clinical sequence 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 33% 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 Decompensated Liver Disease: Among the 174 liver transplant recipients and/or subjects with decompensated 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 who were co-administered HARVONI with sofosbuvir in combination with ribavirin for 12 weeks were treated with HARVONI + RBV. In the ITT population, 353 subjects were on stable antiretroviral therapy. The safety profile in HCV mono-infected subjects. The observations occurred in at least 5% of subjects were headache (20%) and fatigue (17%).

Less Common Adverse Reactions: Adverse events (AEs) reported in less than 5% of subjects receiving HARVONI in any one trial: These events 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 development of systolic arterial hypertension. Patients should be advised to use caution or avoid participation in activities requiring alertness or physical exertion.

HMG-CoA Reductase Inhibitors (cholesterol): High circulating concentrations of LDL can increase the risk of ischemic heart disease. Coadministration is not recommended. See prescribing information for RBV for additional information regarding lactation.

HIV Antiretroviral Therapy: Coadministration (ledipasvir and sofosbuvir) may increase the concentrations of the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John’s Wort) show a variable decrease in ledipasvir concentration. Coadministration with HARVONI is not recommended. The use of HARVONI with certain HIV antiretroviral regimens is contraindicated in pregnant women and breastfeeding women, so patients with severe renal impairment or ESRD. No dosage adjustment of HARVONI is recommended. The safety and effectiveness of HARVONI have not been established in pediatric patients. There are no adequate and well-controlled studies in pediatrics. Safety and effectiveness in pediatric patients below the age of 16 and over (5% of total number of subjects in the clinical studies).

Increased digoxin concentration. Monitor digoxin therapeutic levels in patients with severe renal impairment or ESRD. Safety and effectiveness of HARVONI have not been established in pediatric patients.
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. 1,2

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.

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 hyoscymine) and peppermint oil relieve muscle contractions without really affecting the diarrhoea and are worth a try as an addition to treatment but not as a sole treatment. Colesesalam ( 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 Clostridioides 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 Clostridioides difficile) to re-treat at least two more times (in 10 week intervals). 3 Eluxadoline, a mixed mu opioid agonist and delta opioid antagonist (75,100mcg 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. 4

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 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 this data. The Grohe’s and Collits 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, disease awareness and screening can improve adherences to measures detailed by AGA, and ultimately improve the care we provide to our IBS-D patients.

NEW OPTIONS ON THE HORIZON FOR IBS-D

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

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, professors always make sure the first row of toilets all over the whole campus and I am constantly being asked about the location of toilets all over the whole campus and I am constantly being asked about the location of toilets all over the whole campus and I am constantly being asked about the location of toilets all over the whole campus and I am constantly being asked about the location of toilets all over the whole campus 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 started crying 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 altered bowel function. Currently, IBS is diagnosed using Rome criteria (Rome IV was released in May 2016) and subclassified according to predominant bowel symptoms as IBS-D, IBS-C, and IBS-M. IBS-D is subclassified according to predominant diarrhea and 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 Clostridioides difficile) to re-treat at least two more times (in 10 week intervals). Eluxadoline, a mixed mu opioid agonist and delta opioid antagonist (75,100mcg 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.

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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.

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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, disease awareness and screening can improve adherences to measures detailed by AGA, and ultimately improve the care we provide to our IBS-D patients.

REFERENCES
6. Cornerstones Health has developed a valuable health maintenance checklist at www.cornerstoneshealth.org 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 this data. The Grohe’s and Collits 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, disease awareness and screening can improve adherences to measures detailed by AGA, and ultimately improve the care we provide to our IBS-D patients.
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.

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Since the Human Microbiome Project launched in 2008, we’ve learned from the riches of translational biology — 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 is not the focus of the study, it is associated with a particular disease report. As a result, there is enthusiasm for leveraging the therapeutic potential of the microbiota. The American Gut Project is an attempt to learn before the microscope becomes a treatment option for clinicians. Statistical power is key, and therefore, so are large sample sizes. The American Gut Project\(^1\), 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 17,000 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 Education. At Digestive Disease Week\(^2\) (DDW) 2016, the center hosted a one-of-a-kind session titled Active Learning Session on the Gut Microbiome: 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. 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\(^3\), an adolescent Crohn’s cohort\(^4\), a Chinese Crohn’s disease cohort\(^5\), and a single individual diagnosed with Crohn’s disease with longitudinal samples spanning months\(^6\). We also included a canine IBD dataset to assess species-specific differences and similarities. Leveraging Qita, an open-source microbiome data storage and analysis resource developed in our lab\(^7\), 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). 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 not be noted 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. A recording of the center’s DDW 2016 session is also available at http://www.gastro.org/about/initiatives/AGA-American_Gut/Handout/DDW_2016.pdf.9 Additional analysis and resource development are ongoing. We will continue to share our knowledge and findings with AGA members and health. We will continue to share our knowledge and findings with AGA members and through our collaboration with AGA and additional insights are available on http://www.gastro.org/about/initiatives/AGA-American_Gut. A recording of the center’s DDW 2016 session is also available at http://www.gastro.org/about/initiatives/AGA-American_Gut/Handout/DDW_2016.pdf.9 Additional analysis and resource development are ongoing. We will continue to share our knowledge and findings with AGA members

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 Bacterial Phyla (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 not be noted 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. A recording of the center’s DDW 2016 session is also available at http://www.gastro.org/about/initiatives/AGA-American_Gut/Handout/DDW_2016.pdf.9 Additional analysis and resource development are ongoing. We will continue to share our knowledge and findings with AGA members and through the AGA Center for Gut Microbiome Research and Education.

REFERENCES

1. http://americangastro.org

Figure 1. PCoA plot illustrating the seven datasets analyzed in the current meta-analysis. Each dot represents a single sample and is colored by study: Red = AGA volunteers (“AGA-fecal”); dark blue = American Gut (“AGA-fecal”); orange = canine IBD (“Canine-fecal”); green = Chinese IBD (“Chinese IBD-fecal”); purple = adolescent IBD (“Sevent IBD-fecal”); yellow = individual Crohn’s patient (“Smart IBD-fecal”); and U.S. IBD (light blue, “Sandborn IBD-fecal”). 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 microbiota these samples were more similar to dog samples than to other human samples in the meta-analysis.

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).
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 likelihood of disease, whom the benefit-risk ratio is most favorable—accurate and reproducible risk stratification systems 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 However, the acceptable rate of “negative” ERCP for suspected choledocholithiasis is a value based on multiple factors, including local ERCP expertise and the availability, cost and performance characteristics of alternative diagnostic modalities. Indeed, while conclude from this 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.3 Similarly, surveyed practitioners caring for patients with bile duct disease considered 2.5 (95 percent CI, 2.2–2.8) negative ERCPs per every 10 procedures an acceptable rate.

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, IOC or EUS 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 upfront ERCP in all consort with suspected choledocholithiasis (but no concern for cholangitis) revealed that initial EUS reduced procedure time and adverse events without affecting stone-related outcomes.4 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 endoscopic 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 system aims to risk-stratify patients to undergo cholesctectomy 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 may be cost effective or economic for detecting a small number of patients with suspected gallstone pancreatitis.5 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).6 Unfortunately, none of these models have demonstrated that they can substantially outperform the ASGE guideline in our cohort of approximately 700 patients from two academic institutions.7

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.8,9

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.10 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.11 Third, in patients undergoing cholecystectomy who require ERCP most surgeons prefer that stones be cleared pre operatively, although intraoperative and postoperative ERCP have been shown to be safe and equally effective.12

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 found on existing evidence, but sensitive to the principle of minimizing unnecessary risk, will serve our patients well.

REFERENCES

Upcoming Research Funding Opportunities

The AGA Research Foundation will award over $2 million in research funding to support researchers in gastroenterology and hepatology.

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<td>AGA Research Scholar Award</td>
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