

# AGA Perspectives

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## DO NOT DISTURB

Are gastroenterology and the microbiome ready for probiotics?

Articles by Matthew A. Ciorba, MD; and Peter H.R. Green, MD. [See page 4](#)



## In this issue

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Matthew A. Ciorba, MD;  
Peter H.R. Green, MD.  
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# Note From the Editor



**T**he current issue of *AGA Perspectives* covers a wide variety of emerging topics in the world of GI. There is considerable enthusiasm from our patients for the use of probiotics, but what kind of advice should we provide? This interesting topic is the subject of our featured debate between Drs. Matthew A. Ciorba and Peter H.R. Green. Other hot topics we investigate in this issue include the role, if any, of diet in the management of IBD, dilemmas in HCV therapy in HIV co-infected patients, new drugs for the treatment of acute pancreatitis and the current status of chemoprevention of colon cancer.

Gastroparesis is clearly one of the most vexing problems faced by both patients and gastroenterologists, and Dr. Jay Pasricha provides an update on many of the new insights obtained over close to 10 years of work by the Gastroparesis Clinical Research Consortium. This work has the potential to finally advance therapy for gastroparesis. Another evolving area of GI motility is high-resolution esophageal manometry and Dr. Prakash Gyawali makes a convincing case for the importance of this tool in state-of-the-art esophageal physiology testing. Finally, Dr. Sarah Streett provides an update from the AGA Practice Management and Economics Committee on some of the tools AGA is providing to assist in navigating the ongoing challenges in health-care reform.

Each of these contributions provides updates that will continue to keep readers informed and engaged in the evolving trends in the science and practice of gastroenterology and hepatology.

Thanks for reading,



**Gary W. Falk, MD, MS, AGAF**  
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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](mailto:communications@gastro.org) and include "AGA Perspectives" in the subject line.

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# DO NOT DISTURB

Are gastroenterology and the  
microbiome ready for probiotics?



# Probiotics in GI Disorders



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## PRO

**T**he microbiome is among the hottest topics in medical and scientific research. The National Institutes of Health and private foundations have invested hundreds of millions of dollars in research to define and characterize the human microbiome. In the next decade, billions more will be devoted to deciphering how microbes influence human health in a positive manner. The implications of this field now go well beyond GI tract diseases to include disorders ranging from autism and allergies to obesity. It is indeed an exciting time for those of us in the practice of gastroenterology who should be looked to as leaders in this revolutionary new field. Alas, as with most of science, it takes an extensive amount of time for the translation of preclinical research findings to reach clinical practice. Thus, it is not surprising that of the myriad high-profile discoveries made utilizing sophisticated microbial sequencing technology, none have led to any changes in patient care to date.

In fact, most of the human studies on probiotics that guide our clinical practice today were influenced by the pioneering theories of Elie Metchnikoff from over a century ago. He was the Russian zoologist who first postulated that host-friendly bacteria, such as those found in yogurt, could enhance human health. As a testament to his influence, most human clinical trials and data for probiotics on human health to date have been conducted using milk-fermenting bacteria such as *Lactobacillus* and *Bifidobacteria* species. Although this

**PRO - CONTINUED ON PAGE 6**

## CON

**W**hen considering the role of probiotics in altering the gut microbiome, we have more questions than answers. While my colleague has dutifully pointed out the promise, I have outlined a few problems we would be irrational to ignore.

We recently performed a survey of patients with celiac disease concerning the use of complementary and alternative medicine.<sup>1</sup> Among the respondents, 24 percent claimed they used one or more forms of complementary and alternative medicine, and probiotics were the most frequently used. In this study, these subjects had more symptoms than those who did not take this approach, though they also had a higher quality of life.

Probiotics are manufactured and marketed as dietary supplements. The Dietary Supplement Health and Education Act of 1994<sup>2</sup> effectively minimized regulation by FDA for any product labeled as a dietary supplement. These products are not subject to FDA's rigorous standards of testing, controlled studies and safety requirements like drugs are. Recent articles in the *New York Times*, including an editorial,<sup>3</sup> highlight the state of the dietary supplement industry. In the editorial the description of testing various herbal supplements using bar code DNA testing found that four out of five of the herbal supplements tested did not actually include any of the herbs listed on their labels.

These studies led the New York state attorney general to issue cease and desist orders to four major retailers concerning the sale of these dietary supplements; other states are

**CON - CONTINUED ON PAGE 7**



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## Probiotics have a place in managing GI symptoms and conditions.



### PRO - CONTINUED FROM PAGE 5

background may seem inauspicious, a substantial body of work supports the benefits of these “first-generation” probiotics. Multiple *Lactobacillus* and *Bifidobacteria* species positively influence host physiology through a variety of mechanisms. These include, but are not limited to, competing with gut pathogens, exerting anti-microbial effects, enhancing gut barrier function, modulating motility and sensation, impacting host immune function and contributing to important metabolic functions such as short chain fatty acid production and even drug metabolism. With all these ascribed benefits, it is no wonder that we’ve seen at least some positive human clinical trials using these present day probiotics.

So, where does the data currently support the use of probiotics in clinical practice? The following bullet points summarize the topic:<sup>1</sup>

- Antibiotic-associated diarrhea: Several *Lactobacillus* strains as well as the probiotic yeast *Saccharomyces boulardii* are capable of limiting the duration or intensity of diarrhea associated with taking common antibiotics such as cephalosporins and macrolides. Individuals might consider taking their probiotic supplement at a different time than the antibiotic to enhance the likelihood of probiotic

survival and efficacy. I frequently recommend a reputable *Lactobacillus*-containing probiotic (such as Culturelle) to patients who have experienced this in the past. I also found this strategy to be effective for my own children.

- Infectious gastroenteritis: Bacterial and viral infections can be bothersome not only during the acute phase, but can also lead to bowel irregularity for weeks afterward. Taking a *Lactobacillus* probiotic or *S. boulardii* may shorten the duration of both the acute illness and extended symptoms.
- Irritable bowel syndrome: IBS symptomatology is complex, but several studies suggest certain probiotic products reduce symptoms in some individuals. Align, a specific *Bifidobacteria* strain, improved global IBS scores more than a placebo or a *Lactobacillus* probiotic in one study. In my own practice, I find Align to be helpful for some patients, particularly with bloating and associated dysphoria. The multi-strain probiotic VSL#3 is another option and meta-analysis suggests that *Bifidobacteria* are more effective than *Lactobacillus* strains.<sup>2</sup>
- Inflammatory Bowel Disease: A variety of probiotic preparations

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## CON - CONTINUED FROM PAGE 5

pursuing the same course. This was the culmination of previous articles in the *New York Times* that referred to the work of Newmaster *et al*,<sup>4</sup> who used bar code DNA testing to demonstrate an alarmingly high rate of product substitution, contamination and use of unlabeled, potentially dangerous (to some patients) fillers in commercially obtained herbal supplements in North America. There was a high rate of the presence of products such as rice, wheat and noxious herbs, none of which were on the label. This is hardly a vote of confidence for the industry and its products. The sources were varied and the findings were across products from

from pharmacies and one through a prescription. We then examined them for gluten using liquid chromatography-mass spectrometry;<sup>5</sup> gluten from wheat, rye and/or barley was detected in about half of them. There were greater than 20 parts per million of gluten — the FDA-allowed concentration of gluten below which is regarded as being gluten-free — in several, including some that were labeled gluten-free. However, it is not clear if the small amount of gluten that people with celiac disease taking these products would consume is harmful. For instance, gluten challenge studies reveal that patients exhibit varying degrees of sensitivity to different doses of gluten, however some people with celiac are sensitive to very small quantities.<sup>6</sup> In

Our study and these recent articles in the *New York Times* prompted us to wonder whether there could be gluten in probiotics that may be contributing to the increase in symptoms.

different suppliers and of different price ranges.

Our study cited above, and these recent articles in the *New York Times*, prompted us to wonder whether there could be gluten in probiotics that may be contributing to the increase in symptoms in patients with celiac disease who use probiotics. In light of this, we purchased probiotics of a range of prices and from various sources including Amazon.com, store brands

addition, there is evidence that after a period on the gluten-free diet patients may become more sensitive to small amounts of gluten compared to the time of original diagnosis. The presence of gluten in probiotics labeled gluten free is concerning to those who need to avoid gluten, as they are typically vigilant about everything they consume, and this indicates that they cannot always trust the labels of some products.

## CON - CONTINUED ON PAGE 9



have been studied using varied clinical endpoints for IBD.<sup>3</sup> In short, probiotics have not been found to be beneficial in Crohn's disease. In ulcerative colitis and pouchitis, multi-strain probiotics such as VSL#3 may be effective as an add-on or single agent for some patients with mild or even moderate disease activity. In my own clinical practice, I have found only a few instances of sustained objective success for this strategy.

- **Hepatic Encephalopathy:** Recent intriguing data suggests that single or multi-strain probiotics may improve signs of hepatic encephalopathy and its complications including hospitalization.<sup>4</sup> Confirmative studies will be needed to move this strategy into clinical practice.

While I believe that probiotics have a place in managing GI symptoms and conditions, please consider a few caveats and basic principles when recommending probiotics to your patients:

- Probiotic supplement efficacy is typically moderate as compared to traditional pharmaceuticals. As such, they are often better as a supplement to, rather than replacement for, traditional pharmaceuticals.
- Probiotic strain(s), quantity and preparation make a difference. Multi-strain or even dual-strain probiotics are not necessarily better. For example, several single-strain probiotics effectively reduce antibiotic-

associated diarrhea. However, a large prospective randomized clinical trial recently failed to show antibiotic-associated diarrhea reduction when using a multi-strain *Lactobacillus* and *Bifidobacteria* probiotic product.<sup>5</sup>

- Quality control remains an important issue. My colleague makes this very clear and his remarks certainly apply to a great number of supermarket shelf products. This fact underscores the importance of learning the data and basing your recommendations on reliable brands that have been proven in human clinical trials.<sup>1</sup>
- Probiotics are generally considered to be safe in most patients. This includes IBD patients on TNF- $\alpha$  inhibitors. However, urge more severely immunocompromised patients to avoid probiotics and make sure patients with indwelling catheters do not break open the capsules.

A few final things to consider. First, patients (friends and family members too) may ask you if they should routinely take a probiotic or consume a probiotic yogurt for their "general digestive health." These questions are likely prompted by product labels indicating that their probiotic "improves digestive health" or "strengthens the immune system." These statements are specifically vague as FDA has not approved any health claims for probiotics. I usually respond by encouraging the individual to monitor if his or her own symptom response goals are being met by taking the probiotic for a month. If not, their money is probably better spent elsewhere.

Microbiota-gut-brain interactions are an active area of research that will hopefully lead to new clinical strategies for mood disorders. The specifics of how this strategy might be best employed are still being investigated, but consider this: probiotic studies often find that patients taking the probiotic "felt better" in some way than those taking placebo. This "feeling better" frequently occurred even in the absence of an objective improvement in GI-disorder-related symptoms. For example, my colleague's group recently reported that celiac disease patients taking probiotics had a higher celiac disease related quality of life, even though they experience higher disease symptom scores.<sup>6</sup> So, keep in mind that taking probiotics could actually impact your patient's disease-related quality of life, even without objectively changing their disease symptoms.

I will close by briefly mentioning so-called "next generation" probiotics. While I personally remain optimistic for the translation of these new non-*Lactobacillus* or *Bifidobacteria* probiotics or perhaps probiotic-derived products, many questions remain to be answered. What will their safety profile be? Will they be effective in pill form? Will individual probiotic species be the answer or will novel consortium-based probiotic products be tailored to treat specific diseases as is nearing reality for *Clostridium difficile*?<sup>7</sup> With these questions still looming and patient interest in "first-generation" probiotics at an all-time high, now is a great time to learn more about the supporting data and incorporate them into your practice when appropriate. ■

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With all these questions, I wonder whether we should be advising the use of products that we know so little about.

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Other factors to consider with probiotics include contamination with pathogenic organisms and their safety in immunocompromised individuals. The death of a newborn child in a Connecticut hospital due to the fungal contamination of a prescribed probiotic prompted an official CDC health advisory.<sup>7</sup> How often are probiotics contaminated with other organisms, such as *Candida*, that are obviously not on the label? What quality control measures to determine if contamination exists are practiced by manufacturers? Newborns are considered immunocompromised. Bacteremia due to the specific administered probiotic has been reported in pre-term babies administered probiotics to prevent necrotizing enterocolitis.<sup>8,9</sup> How widely are newborns prescribed a probiotic in the hospital setting? What probiotic does the hospital pharmacist acquire and from where, the corner drug store? Bacteremia has been reported in children with short bowel syndrome as well.<sup>10</sup> Though generally considered safe in children,<sup>11</sup> studies vary in quality and there are questions as to whether adverse events are adequately reported.

The use of probiotics in newborns is controversial.<sup>12</sup>

Another important question is if probiotics should be given to patients taking immunosuppressants or immunomodulatory agents? Patients usually don't volunteer information about medications that are not prescribed as they are not considered medications, merely dietary supplements, so there is a danger that we are not aware of a potential problem. Cochrane analyses of probiotic use in ulcerative colitis reveal them to be generally safe without increase in adverse effects.<sup>13,14</sup>

However, recent reports of bacteremia — due to *Lactobacillus* species that are identical to that in the probiotic — in patients with active colitis receiving steroids and immunosuppressive agents, raises concern for their use in seriously ill patients.<sup>15</sup> Studies have used probiotics in patients with IBS, IBD and celiac disease. No doubt these specific probiotic samples were supplied by the manufacturer. One also wonders whether the probiotics available to consumers are of the same standard as

those supplied to the investigators.

Additionally, I was struck by the fact that only five of the 22 probiotics we purchased in our study had an advisory that they should be refrigerated. This raises further questions about the viability of the organisms in the capsules that are supplied to the consumer. What is the shelf life? Does refrigeration make a difference? At what rate does viability decline and does this matter, as dead microorganisms may convey some health benefit?

Certainly we are all very excited to learn about the microbiome and its role in disease, especially gastrointestinal issues. This knowledge will lead to new therapies that may allow us to alter the microbiome in a beneficial way. However, are we there as yet with our currently available probiotic products? I do not think so. With the questions raised above, I wonder whether we should be advising the use of products that we know so little about, including their manufacturing processes and efficacy. They are not regulated like the other medications we prescribe, so maybe we should be advising patients to avoid them. ■

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Recognizing the vast potential of the gut microbiome, AGA created the AGA Center for Gut Microbiome Research and Education to continue to advance our understanding of the gut microbiome and provide microbiome-related research opportunities.

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# DOES **DIET** INFLUENCE THE DISEASE COURSE IN PATIENTS WITH IBD?

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The pathogenesis of IBD is complex and involves both genetic and environmental factors. Among the environmental factors associated with IBD, diet and the intestinal microbiota would seem the most likely to be modifiable, making them potential targets for disease prevention and treatment. Also, in the past five years, researchers have learned much about the effects of diet on the mucosal immune system, epithelial barrier function and gut microbiota. While these relationships are complex and not fully elucidated, it is clear that dietary nutrients can directly regulate immune function as well as modify the composition of the gut microbiota and its production of metabolites, which can have subsequent effects on the host.

IBD has also been demonstrated by studies suggesting that dietary milk fat and more recently, dietary emulsifiers — which are additives found in most processed foods — can exacerbate colitis in a mouse model of IBD.

We know that diet is important to patients who have IBD. “What should I eat?” is one of the most commonly asked questions by patients and is also one of the most difficult to answer. Patients often identify foods that cause increased symptoms and subsequently follow self-imposed restricted diets. However, for the most part, there is not clear evidence for a direct link between these dietary alterations and the reduction in inflammation. The available evidence suggests that diet may play an

of post-operative recurrence. Although the mechanism of action of enteral nutritional therapy has not been well-characterized, hypotheses involve reduction in luminal antigens secondary to food exclusion (i.e., excluding something potentially harmful from the typical diet) and modulation of the gut microbiota. Newer exclusion diets — such as Chiba and colleagues’ semi-vegetarian diet to prevent relapse, and Levine and colleagues’ Crohn’s Disease Exclusion Diet to induce remission — have demonstrated efficacy in small populations of Crohn’s patients, providing additional support for the notion that there is something harmful in the typical diet that leads to inflammation or dysbiosis and

“What should I eat?” is one of the most commonly asked questions by patients and is also one of the most difficult to answer.

Now, we know that the incidence of IBD is highest in industrialized nations; and in developing nations, where IBD was once rare, the incidence has increased as these nations have become more industrialized. This has led to the hypothesis that increased IBD incidence is associated with westernization, particularly the consumption of a western diet. There are in fact epidemiologic data associating dietary patterns consistent with a western lifestyle with an increase in disease risk. For example, high dietary intake of total fats, polyunsaturated fatty acids, omega-6 fatty acids and meat has been associated with an increased risk of both Crohn’s disease and ulcerative colitis. We have also learned from the Nurses’ Health Study, a large cohort of registered nurses in the U.S., that long-term intake of dietary fiber is associated with a decreased risk of developing Crohn’s disease. These findings support the hypothesis that diets high in fruits and vegetables, and low in meats and fats, may reduce the risk of developing IBD. The notion that diet, particularly the western diet, may be involved in the pathogenesis of

important role in disease pathogenesis, but can diet alter the disease course once the IBD diagnosis has been made?

I am convinced that the answer is “yes” and the strongest evidence to support this belief is the success of defined formula diets for the treatment of Crohn’s disease. In Crohn’s disease, exclusive enteral nutrition with various formulas has been utilized for nearly four decades and is considered first-line therapy for the induction of remission in many parts of the world. Exclusive enteral nutrition has been shown to promote mucosal healing in Crohn’s disease and there are obvious additional benefits, such as the lack of serious adverse events that can be associated with corticosteroids and other pharmacologic therapies, as well as the positive impact on nutrition and bone health. While the majority of the evidence supports a role in the induction of remission in Crohn’s disease, there is also some evidence to suggest that specific enteral nutritional therapy protocols may be efficacious in the maintenance of remission and prevention

exacerbating IBD.

The Crohn’s Disease Exclusion Diet, for example, excludes foods that are commonly thought of as being more prevalent in the western diet and also foods which have been shown to be pro-inflammatory in animal models of IBD. It is important to note that these and other exclusion diets, such as the specific carbohydrate diet, have not been sufficiently studied. But it is reasonable to hypothesize that diets that are less restrictive than exclusive enteral nutrition may alter the disease course and may soon be a part of our treatment armamentarium.

Going forward, we need to improve our methods for studying diet in IBD and we also need to better understand the mechanism of action of exclusive enteral nutrition, which will inform the development of new dietary therapies to control these diseases. ■

# HIV/HCV CLOSING THE GAP



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Medicine Residency Program

*Dr. Chan has no conflicts to disclose.*

**P**atients who are co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) have long represented a special population of patients with a unique set of challenges and barriers to HCV treatment access. FDA identifies HIV/HCV co-infected patients as a population with an unmet medical need due to the more rapid progression of liver disease reported in the highly-active antiretroviral era and the lower reported sustained virologic response (SVR) rates to pegylated interferon and ribavirin (PEG/RBV) treatments.

In the days of interferon and ribavirin, HIV/HCV patients faced significant barriers to therapy, including high rates of psychiatric disease and substance use, competing co-morbidities and greater treatment complications. The past few years have brought a shift in the HCV treatment paradigm to oral, combination direct-acting antiviral (DAA) therapies, which offer a greater than 90 percent cure for all. This exceptional medical advancement has closed the gap of HCV treatment response for HIV/HCV patients. In fact, current U.S. and European HCV guidelines report that the treatment of HIV/HCV and hepatitis C infection should not differ. As HIV becomes less relevant for HCV treatment efficacy, there remain differences between these populations that are important to consider.

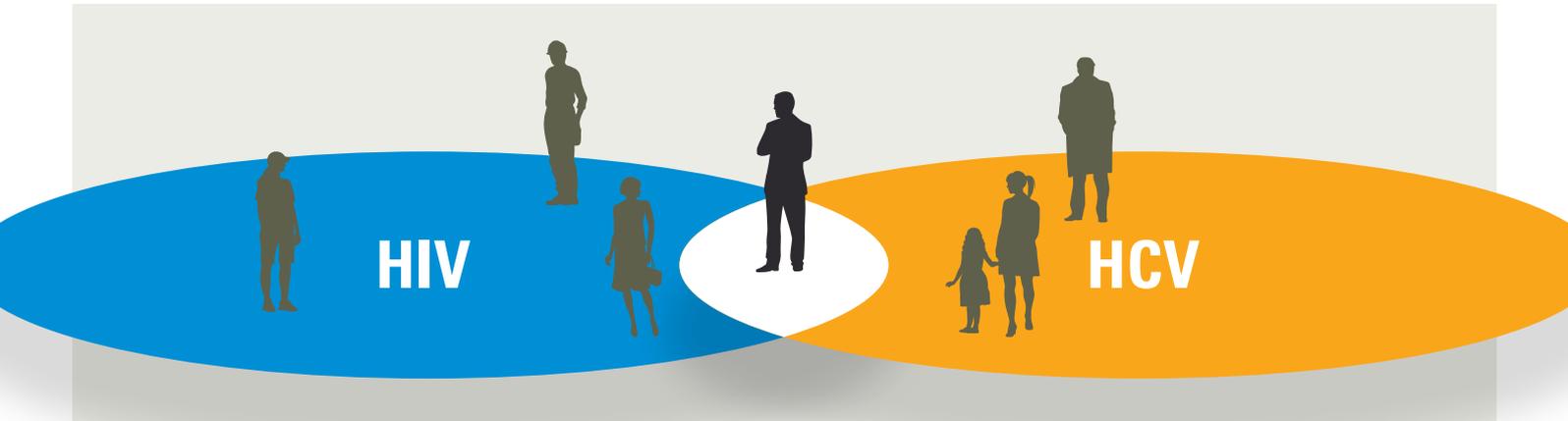
When left untreated, HIV/HCV co-infected patients face more rapid progression of their liver disease to cirrhosis and the associated complications, including hepatic decompensation and hepatocellular carcinoma. The recent D:A:D cohort reported that liver disease remains a leading cause of death in patients living with HIV and that HCV infection is independently associated with all-cause mortality.<sup>1</sup> Furthermore, a recent model of liver disease in HIV/HCV patients suggested that waiting until these patients have

stage F2 or more severe fibrosis to achieve cure increases the risk of hepatitis C-related mortality.<sup>2</sup> For this reason, the AASLD/IDSA HCV treatment and management guidelines identify HIV/HCV patients as high priority for HCV treatment access, regardless of liver disease stage. This is a critically important point when interacting with payors who are denying access to HCV treatment for patients with lower stages of liver fibrosis. In our clinic, we consider every HIV/HCV patient for HCV treatment regardless of liver disease stage, but access has not been as universal as we would have hoped for this high-risk population. For those patients with decompensated liver disease, transplantation prior to therapy is recommended because the wait times are more favorable when obtaining an HCV-positive organ for most United Network for Organ Sharing regions.

Although historically HIV/HCV patients experienced lower SVR rates with PEG/IFN, trials of DAA combination therapies have convincingly shown that this is no longer the case. There are now four Phase 3 trials of oral DAA regimens in HIV/HCV patients that have reported the same SVR as those reported in HCV mono-infected patients, regardless of prior treatment experience and presence of cirrhosis.<sup>34</sup> Similar to HCV mono-infected patients, HIV/HCV patients can expect greater than 95 percent cure rates when treated with DAA combination therapies. Based on these data, the U.S. and European guidelines recommend that HIV/HCV patients be treated the same as patients without HIV infection.

In addition to achieving similar cure rates with DAA combination therapy, Phase 3 studies have found that adverse events and treatment discontinuations are the same for HIV/HCV and HCV-infected patients. To date there is no evidence that HIV/HCV patients have differences in baseline resistance to DAAs or response rates than

# The DAA era in HCV therapeutics has revolutionized the way we approach the management of patients coinfecting with HIV/HCV.



patients with baseline variants. However, DAA combination therapies do bring a challenge for HIV/HCV patients that does not exist to the same extent for HCV mono-infected patients: drug interactions. Drug interactions with antiretrovirals and DAAs are common, complex and can result in limited HCV treatment options, especially for HIV/HCV patients on more complex salvage HIV regimens. Communication between a patient's HCV provider and their primary HIV provider is of the utmost importance in choosing an HCV regimen and preventing drug interactions. Yet as more DAAs are approved by FDA and because the efficacy of these regimens are similar, even this current challenge will be overcome.

One challenge that we will face in the management of HIV/HCV patients is reinfection in those patients with ongoing risk behaviors. Cohort studies suggest that HIV coinfection increases the risk of hepatitis C transmission, especially in

HIV-infected men who have sex with men. Recent data have demonstrated the real and significant risk of HCV reinfection in the co-infected population with rates as high as 21.8 percent as compared with their mono-infected cohort who demonstrated rates of 1 percent and 8 percent in low- and high-risk groups, respectively.<sup>5</sup> While these studies only reflected small sample sizes, the rates of reinfection were high enough to indicate that education regarding reinfection and risk behaviors will be critical at the end of treatment. Furthermore, when treating a patient whose sexual partner is known to be HCV infected, attention to education and encouraging the partner to seek hepatitis C treatment is important to decrease the risk of reinfection.

The DAA era in HCV therapeutics has revolutionized the way we approach the management of patients co-infected with HIV/HCV. DAAs have rendered HIV less relevant in the consideration

of HCV therapy efficacy and safety, but the population is still unique given the accelerated natural history of liver disease and the complex drug interactions related to concomitant antiretroviral therapy. While drug interactions will still remain, the ability to address these with either ARV switches or the increasing number of available highly efficacious DAA regimens limits the impact on access to therapy. While HCV eradication significantly decreases the risk of liver-disease-related complications, the risk of progression of liver disease due to other liver injuries is less clear. The management of HIV/HCV patients post cure should focus on monitoring for signs of ongoing liver injury (ARV toxicity, steatosis) as well as education and screening for reinfection in those patients with ongoing risk. For those patients who suffered from severe liver disease, long-term follow up for hepatocellular carcinoma screening and cirrhosis management will remain. ■

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# Updates from the Gastroparesis Clinical Research Consortium



**Pankaj Jay Pasricha, MD**

Vice Chair of Medicine for Innovation and Commercialization, Director, Johns Hopkins Center for Neurogastroenterology  
Professor of Medicine and Neurosciences; Professor of Innovation Management, Johns Hopkins Carey School of Business

*Dr. Pasricha holds equity in several companies in the gastroenterology field.*

**G**astroparesis is a complex medical problem associated with a significant degree of morbidity and suffering. In 2006, the National Institute of Diabetes and Digestive and Kidney Diseases established the Gastroparesis Clinical Research Consortium (GPCRC) to advance the knowledge of the natural history of gastroparesis, its pathophysiology and pathogenesis, and therapy; with the goals of (a) building a large registry and bio-repository from carefully phenotyped patients and (b) performing rigorous treatment trials. Through these studies, the consortium has confirmed the burden and persistence of illness in these patients and has identified several factors associated with prognosis. Surprisingly, we found that obesity is common among patients with gastroparesis and is associated with differences in clinical phenotype with a worse outcome. Further, small bowel and colonic dysmotility are seen in a significant number of patients.

Critical new knowledge has also been gained in several other areas. Thus, we now have good insight into the pathological basis of gastroparesis. Analysis of full-thickness gastric biopsies shows that the major cellular defect involves interstitial cells of Cajal (ICC) and not neurons or smooth muscle. Further, ICC loss correlates with delays in gastric emptying. These changes are accompanied by a significant pro-inflammatory macrophage infiltrate, suggesting an underlying immune dysregulation as the driving factor. Other studies have shown that molecular variants in the key ICC ion channel, Ano-1, are more prevalent in diabetic patients with gastroparesis than in those without it. These advances have, for the first time, raised hopes for rational, disease-modifying therapy. Thus, specific drugs that address ICC loss, dysfunction or channelopathies/arrhythmias could potentially be very useful in treating gastroparesis. Other new pharmacological approaches that could go even further include suppression of the macrophage-driven immune

While awaiting these exciting future developments, it is important to find more immediate solutions to relieve the suffering that so many of these patients undergo on a daily basis.

response that may underlie these changes, raising the hope for a real cure.

While awaiting these exciting future developments, it is also important to find more immediate solutions to relieve the suffering that so many of these patients undergo on a daily basis. A major objective of the consortium is to conduct rigorous trials of such drugs so that their widespread use can be supported. Unfortunately, the Nortriptyline for Idiopathic Gastroparesis (NORIG) trial conducted by the GPCRC failed to demonstrate the efficacy of low-dose nortriptyline, an antidepressant and neuromodulator, which is used based on the hypothesis that visceral hypersensitivity plays a significant role in the pathogenesis of symptoms. Our hopes are now centered on the results of the recently concluded Aprepitant for the Relief of Nausea in Patients With Chronic Nausea and Vomiting of Presumed Gastric Origin Trial (APRON) trial that examined the efficacy of aprepitant, an inhibitor of the neurokinin-1 receptor, currently indicated for the treatment of chemotherapy-induced nausea and vomiting.

Diabetic gastroparesis, although similar in some ways to the idiopathic variety, poses its own unique

challenges for management, particularly with respect to insulin-dependent diabetes. In general, endocrinologists have struggled with the question of aggressive insulin management in such patients, fearing the risk of hypoglycemia from unpredictable gastric emptying of ingested calories. The GPCRC looked at this issue in its Continuous Glucose Monitoring and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT) trial, which required patients to be treated with an insulin pump and continuous glucose monitoring. Preliminary results, presented at Digestive Disease Week® 2015, show that such an approach is safe and not only improves glycemic control but is also associated with improvement in gastroparetic symptoms.

Other results may have far-reaching implications for the field of gastrointestinal motility, including the traditional divide between “organic” and “functional” disorders. Thus physicians have conceptually categorized patients with otherwise unexplained gastric symptoms (nausea and vomiting, along with early satiety and postprandial

## Consortium Contributors

### Clinical Sites

**Johns Hopkins University** (PJ Pasricha, J Clarke, S Dhalla, E Stein)

**Temple University** (H Parkman)

**University of Louisville** (T Abell)

**Wake Forest University** (K Koch)

**Texas Tech University** (R McCallum, I Sorastiek)

**Stanford University** (L Nguyen)

**California Pacific Medical Center** (W Snape)

### Data Coordinating Centers

**Johns Hopkins Bloomberg School of Public Health** (J Tonascia)

### Pathology Resource Center

**Mayo Clinic, Rochester** (G Farrugia, M Grover)

### NIDDK

F Hamilton

discomfort and distention) on the basis of a gastric emptying test. If this is delayed, the patient is diagnosed as having gastroparesis. If normal, the label that is most often applied is functional

dyspepsia, described in GPCRC studies as CUNV (chronic unexplained nausea and vomiting). We have shown that these patients are clinically indistinguishable from those with delayed gastric emptying in terms of both the nature and severity of symptoms, and further clinical outcomes at one year and beyond are similar regardless of gastric emptying. Emerging data now suggests that macrophage infiltration and ICC loss, albeit to a lesser extent, are similar to what is observed in classical gastroparesis. So it is possible that patients with gastroparesis and at least some patients with “functional dyspepsia” are part of a broader spectrum of gastric neuromuscular disease.

In summary, the GPCRC has provided a detailed understanding of the clinical characteristics and course of patients, has identified specific pathological changes and has implicated putative etiologies, setting the stage for disease-modifying therapy. Together with planned future research, these results are expected to eventually transform the outcomes for our patients. ■

## Classifieds

### CALIFORNIA

Our medical group is seeking to add another partner to our practice. We are located in San Luis Obispo County, California, a coastal community near Pismo Beach, Avila Beach and Paso Robles. The area has a moderate climate, offers a unique array of outdoor/ cultural activities, and is recognized as a premier wine growing area in the country.

We are interested in a gastroenterologist with excellent endoscopic/ clinical skills, and proficiency in ERCP.

Please mail CV to CCGMG, Attn:

**Dr. Vance Rodgers**, 1551 Bishop Street, Suite 230, San Luis Obispo, CA 93401, or fax to (805) 786-4220.

### ILLINOIS

Seven-physician GI group in suburb of Chicago seeks gastroenterologist to join busy growing practice (in Oak Lawn and New Lenox). Group has two endoscopy centers and own pathology lab. Group has ERCP/EUS, thus these skills are optional. Email CV to [williamt@southwestgastro.com](mailto:williamt@southwestgastro.com).

### MARYLAND

Well-established GI practice of five gastroenterologists is seeking to recruit a full-time BE/BC gastroenterologist to meet increasing clinical demand. This reputed group has served Harford and adjacent counties north of Baltimore for 30 years. Opportunity highlights include:

- Market competitive salary
- Partnership in two years
- Full benefit package including: relocation assistance, malpractice, CME reimbursement and 401k retirement plan
- Call every sixth week
- Electronic Health Record using gMed
- Dedicated endoscopy center
- Infusion center and other ancillary services
- 24/7 hospitalist coverage

Harford county was named one of “Best Places to Live in Maryland,” and boasts excellent schools, low crime rate and great neighborhoods.

Contact: **Dawn Noonan** at (443) 643-4724 or email CV to [dnoonan.harfordgi@yahoo.com](mailto:dnoonan.harfordgi@yahoo.com).

FOR TREATING CHRONIC HCV GT 1 IN ADULTS

# BE THE ONE

WHO CAN CHANGE WHAT'S POSSIBLE

*Albert Einstein*

Albert Einstein used with permission of the HUJ/GreenLight.

## INDICATION

HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 (GT 1) infection in adults.

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

 **HARVONI**<sup>®</sup>  
ledipasvir/sofosbuvir  
90 mg/400 mg tablets



## HARVONI IS THE FIRST AND ONLY SINGLE-TABLET REGIMEN FOR HCV GT 1 PATIENTS BUILT ON A SOFOSBUVIR BACKBONE<sup>1</sup>

# 1

1 TABLET ONCE A DAY  
WITHOUT IFN OR RBV

### Recommended treatment duration for HARVONI<sup>1</sup>:

**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

- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir<sup>1</sup>

IFN = interferon, RBV = ribavirin, TE = treatment-experienced (patients who failed treatment with either Peg-IFN alfa + RBV or an HCV protease inhibitor + Peg-IFN alfa + RBV), TN = treatment-naïve

## HARVONI DELIVERED HIGH CURE (SVR) RATES IN A BROAD RANGE OF GT 1 SUBJECTS<sup>1,a</sup>

# 97%

OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS<sup>1-4,a</sup>  
(n=1042/1079)

- Overall cure rates were 94%-99% in the HARVONI Phase 3 clinical trials<sup>1</sup>
- The HARVONI clinical trial program enrolled the most challenging subjects, regardless of GT 1a or 1b subtype, prior experience with therapy, or presence of cirrhosis<sup>1</sup>

<sup>a</sup> Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.<sup>1</sup> Achieving SVR is considered a virologic cure.<sup>5</sup>

**Study Designs:** **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. SVR rates for all subjects enrolled in the 24-week treatment groups (N=434) were not available at the time of interim analysis. **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

- **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.
- **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 (SOVALDI®).

BE THE ONE WHO CAN CHANGE WHAT'S POSSIBLE.  
GO TO [HARVONI.COM/HCP\\_J1](http://HARVONI.COM/HCP_J1)

## HARVONI WAS SAFE WITH LOW RATES OF DISCONTINUATIONS AND ADVERSE EVENTS (AEs) ACROSS CLINICAL TRIALS<sup>1-4</sup>



### DISCONTINUATIONS DUE TO AEs<sup>1</sup>

- Adverse reactions (all grades) reported in  $\geq 5\%$  of subjects receiving 8, 12, or 24 weeks of treatment with HARVONI: fatigue (13%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%)<sup>1</sup>
- No hematologic monitoring or dose adjustments are required with HARVONI<sup>1</sup>

## MORE THAN 110,000 PATIENTS HAVE BEEN PRESCRIBED HARVONI IN THE US<sup>6,b</sup>



### PRESCRIBED HCV TREATMENT IN THE US<sup>6,c</sup>

<sup>b</sup>This information is derived from IMS NPA Market Dynamics, IMS NPA Monthly data, IntegriChain DNA National, and 867 data; data reflect estimated patient starts from October 2014–April 2015.

<sup>c</sup>IMS Weekly NPA Market Dynamics from week-ending 10/24/14–5/15/15.

## HELP YOUR PATIENTS GET STARTED ON HARVONI WITH SUPPORT PATH<sup>®</sup>



- 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 ( $\geq 10\%$ , all grades) adverse reactions were fatigue and headache.

### 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 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 for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

**CONTRAINDICATIONS:** None

## **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 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.

**Related Products Not Recommended:** Use of HARVONI with products containing sofosbuvir (SOVALDI®) is not recommended.

## **ADVERSE REACTIONS:**

The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials in subjects with genotype 1 CHC with compensated liver disease (with and without cirrhosis) who received HARVONI for 8 (N=215), 12 (N=539) and 24 (N=326) weeks. Adverse events led to permanent treatment discontinuation in 0%, <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): The most common adverse reactions (≥10%; all grades) were fatigue and headache.

Adverse reactions (all grades; majority Grade 1) observed in ≥5% of subjects by treatment duration were:

- *HARVONI for 8 weeks:* fatigue (16%); headache (11%); nausea (6%); diarrhea (4%); and insomnia (3%)
- *HARVONI for 12 weeks:* fatigue (13%); headache (14%); nausea (7%); diarrhea (3%); and insomnia (5%)
- *HARVONI for 24 weeks:* fatigue (18%); headache (17%); nausea (9%); diarrhea (7%); and insomnia (6%)

Direct comparison across trials should not be made due to differing trial designs.

**Laboratory Abnormalities: Bilirubin Elevations:** Bilirubin 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. **Lipase Elevations:** Transient, asymptomatic lipase elevations of greater than 3x ULN were observed in <1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. **Creatine Kinase:** Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

## **Postmarketing Experience**

**Cardiac Disorders:** Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI during post approval use of HARVONI. 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.

## **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. **An 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<sub>2</sub>-receptor antagonists:** Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI.

## Brief Summary (cont.)

- **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) and an HIV protease inhibitor/ritonavir (emtricitabine/tenofovir DF plus atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir):* The safety of increased tenofovir concentrations has not been established. Consider alternative HCV or antiretroviral therapy. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.
  - *Efavirenz/emtricitabine/tenofovir DF:* Monitor for tenofovir-associated adverse reactions. Refer to VIREAD, TRUVADA or ATRIPLA 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 individually: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir DF or verapamil.

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

## USE IN SPECIFIC POPULATIONS:

**Pregnancy:** HARVONI is Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk but had no effect on nursing pups. It is not known if HARVONI and its metabolites are secreted in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the nursing child from the drug or from the underlying maternal condition.

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

**Geriatric Use:** Clinical trials of HARVONI included 117 subjects aged 65 and over. 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<sup>2</sup>) 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). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

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# Inside the AGA Practice Management and Economics Committee



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Practice Management and  
Economics Committee

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Imagine that most of us involved in the practice of clinical gastroenterology feel like an unsought quest has been thrust upon us. In the history of health care in America, there has never been as great an alteration in the practice of medicine as the shift that is taking place beneath our feet.

The paradigm of health care is being transformed from a fee-for-service model into one in which value will be defined by patient satisfaction, outcomes and cost. In many journeys, the protagonist does not choose the voyage, it chooses them. All great quests involve uncertainty and risk. Opportunity and progress are the motivators to persevere; they are also the rewards.

In the face of these seismic changes, the charge of AGA's Practice Management and Economics Committee, in concert with the AGA Institute Roadmap Task Force, is to provide clinicians with a survival kit to succeed in navigating health-care reform. The tools that we have developed and will continue to develop fall into three categories: tools to expand the scope of GI practices, tools to help deliver high-value patient care and tools to help us maximize our revenue.

Opportunities for GI practices to expand are being developed in non-procedural service lines. Our current focus is on the epidemic of obesity, which represents one of modern health care's greatest challenges. Comprehensive care of the obese patient is an area well suited for gastroenterology. Not only are many common GI conditions a consequence of obesity, but also the integral relationship of diet to digestive diseases has historically linked nutrition to gastroenterology.

Two endoscopically placed bariatric devices have been approved in the past several months, and more will undoubtedly follow. These will be potentially important interventions to augment obesity treatment. In order to be the providers of these new technologies and incorporate them into GI practice, comprehensive weight management programs are required to support both patient safety and device efficacy. Our committee, as part of a larger AGA initiative, is developing a multi-disciplinary user's guide on how to safely and effectively implement these new advances of endoscopic bariatric therapy into practice. AGA has taken a collaborative approach in this multi-disciplinary space, and this initiative will be a multi-society effort in conjunction with our colleagues in SAGES, the Obesity Society and NASPGHAN.

Another tool our committee created to help practices move forward is the Benchmark Database project. GI practices that participate in the AGA Benchmark

survey will be able to compare themselves with other groups both regionally and nationally. In addition to basic practice characteristics of size, composition and affiliation, data will be available on reimbursement patterns, Medicare participation, services offered and quality reporting. This resource will be incorporated into a dynamic, easily searchable tool that will allow GI practices to evaluate themselves alongside their peers in order to be informed of current practice trends.

Communication is a vital part of providing high-quality patient care and achieving successful outcomes. We are developing a tool for specialist-to-specialist communication for the management of anti-coagulation at the time of endoscopy. This will be endorsed by both AGA and the American Heart Association. We are also considering similar provider-to-provider communication tools for the management of diabetes and for recommending health-maintenance care for patients with chronic IBD and liver disease. Lastly, we are developing an infographic and video to help patients understand what constitutes a high-value colonoscopy. ([www.gastro.org/QualityCRC](http://www.gastro.org/QualityCRC))

As reimbursement transitions to value-based care, alternative payment models that allow us to be rewarded for demonstrating high quality, efficiency gains and effective care coordination are needed. The AGA Roadmap Oversight and Practice Management groups have developed tools to navigate this transition. In the AGA Roadmap Toolbox, a timeline to value-based care serves as a guide for key transitions ahead. A bundled framework for colonoscopy was published for implementation and supported by an AGA colonoscopy bundled payment discussion forum on LinkedIn. Currently, a GERD bundle framework is awaiting publication. Notably, behind the scenes, the coverage and reimbursement subcommittee of our committee has been instrumental in advocating for the value of our clinical work. They tirelessly lobby and proactively support the evolution of fair and thoughtful payor policies related to all aspects of GI practice.

In order for tools to be useful, they need to be rapidly accessible, flexible and well designed. Going forward, a new focus will be placed on the impact of the Medicare Access and CHIP Reauthorization Act of 2015, and on the needs of the growing number of employed physicians, young gastroenterologists and, importantly, the patients that we care for. The AGA Practice Management and Economics Committee is excited to develop tools that will help AGA members survive and thrive as we navigate the rapidly changing health-care environment. ■

# HIGH-RESOLUTION MANOMETRY

## Are There Any Viable Alternatives?



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**H**igh-resolution manometry (HRM) was conceived by Ray Clouse to overcome gaps in esophageal pressure data acquisition, display and interpretation. HRM utilizes closely spaced circumferential sensors on an esophageal manometry catheter to collect pressure recordings. Software programs interpolate best fit data between acquired raw pressure data and assign colors to amplitudes to generate seamless topographic plots of pressure phenomena (Figure 1A). The topographic color plots are known as “Clouse” plots in Ray Clouse’s honor.<sup>1</sup>

Before high resolution manometry there was conventional manometry, with five to eight data sensors displaying point pressure in the form of stacked line tracings. A prominent disadvantage was the stationary pull-through maneuver; the process of locating the esophagogastric junction and its components. Modern HRM systems eliminate this maneuver, as pressure activity from the entire esophagus is visible and catheter position can be modified in real time to ensure

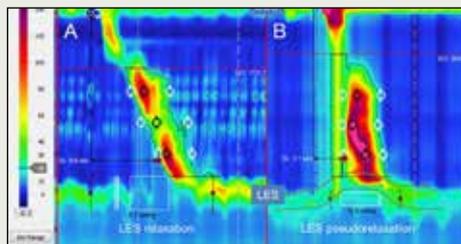
the esophagogastric junction is traversed. The dynamic respiratory pressure signature of the lower esophageal sphincter (LES) and the crural diaphragm define esophagogastric junction morphology, and esophageal length can also be easily determined.<sup>2</sup>

A profound advantage of HRM over conventional manometry lies in the utilization of software tools to interrogate pressure data, particularly at the esophagogastric junction. The integrated relaxation pressure (IRP) measures nadir pressure during swallow induced lower esophageal sphincter relaxation. The LES can be followed proximally when the esophagus shortens, ensuring that the IRP is always measured appropriately (Figure 1B), enhancing identification of esophageal outflow obstruction. Esophageal body software tools assess vigor of smooth muscle contraction (distal contractile integral, DCI) and timing of the peristaltic sequence (distal latency, DL). Using these three software tools, esophageal motor processes have been classified into disorders with EGJ

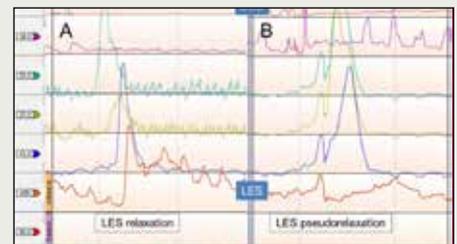
outflow obstruction (including achalasia), major motor disorders not encountered in health, and minor motor disorders with transit abnormalities that are not pathognomonic of disease states. This so-called Chicago Classification has brought uniformity to nomenclature and reporting of esophageal motor phenomena.<sup>3</sup> New software metrics such as the EGJ contractile integral (EGJ-CI) are under study for evaluation of the EGJ barrier. Provocative measures, including multiple rapid swallows, free-water drinking or test meals, stress the esophagus when symptoms are not easily explained, and can uncover motor patterns not evident with routine water swallows.<sup>2,3</sup> Finally, 3D HRM (higher sensor density in a short catheter segment that allows sector averaging of recorded pressures) generates a three-dimensional pressure profile of selected areas, particularly the EGJ where distinct EGJ asymmetry has been identified at rest and during inspiration. These software tools and provocative options cannot be utilized in a similar fashion with conventional manometry.

Non-manometric alternatives to evaluating esophageal symptoms provide additional information that can complement but not replace HRM. For instance, endoscopy with biopsy and endoscopic ultrasound can help exclude a structural basis for esophageal outflow obstruction, especially when esophageal body motor patterns are not typical for achalasia. Barium studies, particularly with solid bolus swallows, can cause structural esophageal lesions. Additional barium findings of clinical value include abnormal esophageal emptying, barium column height in the upright position (i.e. timed upright barium study) and EGJ morphology (i.e. hiatus hernia, achalasia, strictures). The addition of impedance and impedance planimetry to topographic representation of esophageal pressure phenomena continue to be studied as adjuncts to standard HRM. Impedance planimetry using the functional luminal imaging probe can measure cross sectional

**Figure 1.** Swallows A (normal peristaltic sequence) and B (premature sequence with abnormal LES relaxation) are shown on both high resolution manometry (figure 1) and conventional manometry (figure 2). The premature sequence (B) appears to be preceded by relaxation of the lower esophageal sphincter (LES) on conventional manometry. However, abnormal LES relaxation and esophageal shortening can be identified on HRM, leading to the diagnosis of type 3 achalasia.



**A. High-resolution manometry**



**B. Conventional manometry**

## HRM represents a distinct advance over previously utilized motility systems, and continues to evolve.

areas, providing information on elasticity and compliance. The functional luminal imaging probe can assess adequacy of EGJ disruption in achalasia, compliance of the EGJ in reflux disease (especially following fundoplication) and esophageal sensitivity to distension.

For the uninitiated, high resolution manometry may seem challenging, another new complicated technique to master. While even experts may not agree on the subtleties of the Chicago Classification of motor disorders, novice and intermediate trainees preferred high resolution manometry to conventional manometry when offered studies in both formats following a tutorial describing the two methods.<sup>4</sup> Pattern recognition allows for easy recognition of achalasia and major motor disorders, and indeed, such recognition was retained at a three-month follow-up assessment.<sup>4</sup> Another study comparing the two methods reported much higher

accuracy with high resolution manometry compared to conventional manometry in both novice and expert reviewers.<sup>5</sup> Intermediate and novice trainees could identify normal from abnormal motor patterns with management recommendations after teaching and supervised review of 15 to 25 studies.<sup>6</sup> The role of the operator in obtaining pristine, artifact-free studies is crucial, and visual review of the motor patterns is essential in corroborating diagnoses suggested by an automated and computerized review of studies.

High resolution manometry therefore represents a distinct advance over previously utilized motility systems, and continues to evolve. The accuracy of high resolution manometry interpretation may be tempered by the quality of the studies (which is directly related to the skill of the operator), the corroboration of automated analysis with direct visual review, and the diligence of the motility expert in identifying abnormalities that can explain symptoms. Nevertheless, high resolution manometry is here to stay, and there is no viable alternate method of evaluating esophageal motor function that can replace it in the near term. ■

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# IS THERE A DRUG ON THE HORIZON



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**A**cute pancreatitis is a serious disease and is the most common gastrointestinal cause of hospital admission. While the majority of patients present with a mild disease requiring only a short hospital stay, about 20 to 30 percent of patients develop moderate to severe disease, associated with higher morbidity and mortality rates, and larger associated health-care costs.

While current medical management of acute pancreatitis still focuses on supportive care — including fluid resuscitation, pain control, nutrition support and treatment of local or systemic complications — advances in basic research and a better understanding of the pathophysiology in pancreatitis has led to the development of some potential pharmacologic therapies that target the various steps in the pathogenesis of the disease. However, we have to emphasize that there is no firm evidence so far to advise any drugs in clinical use and all the discussion below is about emerging information.

Premature trypsin activation is considered an early event in the development of acute pancreatitis. Somatostatin is a hormone that inhibits basal and stimulated pancreatic enzyme secretion. Conflicting results have been reported using somatostatin or its analogues in acute pancreatitis management since 1980. The largest prospective multicenter randomized study showed no benefit of octreotide in the treatment of acute pancreatitis in terms of mortality, complications, duration of pain, the need of surgical interventions or the length of the hospital stay.<sup>1</sup> However, a recent study from China showed high-dose octreotide administration within 48 hours of onset of acute pancreatitis appears to reduce the risk of developing severe acute pancreatitis and partly attenuate severe acute pancreatitis. In another study, TNF- $\alpha$ , IL-6, IL-10, APACHE II scores, incidences of sepsis, multiple organ dysfunction and mortality were significantly

lower in the somatostatin group compared to placebo.<sup>2</sup> These studies have limitations and currently octreotide or somatostatin cannot be recommended as treatment for acute pancreatitis.

Proteases are potential effective targets for acute pancreatitis therapy as they are markedly activated in severe acute pancreatitis and their activation is related to vasospasm, microthrombosis and pancreatic necrosis. Aprotinin is the first protease inhibitor used in clinical trials for acute pancreatitis. However, no benefits were observed when administered either intravenously or intraperitoneally.<sup>3-6</sup> Intravenous delivery of the newer generation of protease inhibitors gabexate mesylate (FOY), nafamostat mesilate and ulinastatin have demonstrated a reduction in complications and mortality but the trials are very small and metaanalysis failed to show benefits of these medications.<sup>7-9</sup>

Continuous regional intra-arterial infusion (CRAI) delivers medicine through one of the arteries that supplies the affected pancreas, therefore the drug concentration in the pancreas can reach up to 32 times higher with minimal toxic effects compared to routine intravenous administration. Clinical trials have shown that nafamostat mesylate (FUT-175), a broad spectrum protease inhibitor through CRAI and imipenem, resulted in a quicker resolution of abdominal pain, systemic inflammatory response syndrome resolution, lowered serum C reactive protein and the IL6/IL10 ratio, decreased the need for surgical therapy, decreased pancreatic necrosis infection, shortened hospitalization time, and reduced mortality in patients with severe acute pancreatitis.<sup>10-13</sup> CRAI therapy should be initiated within 48 hours after the onset of acute necrotizing pancreatitis.<sup>14,15</sup>

However, these studies also have methodologic problems and meta-analysis of 2 RCTs did not show

# ZON FOR ACUTE PANCREATITIS?

a significant reduction in mortality. Thus, this invasive therapy is not recommended unless future, better-conducted trials show a benefit.

Another promising pharmacological target is TNF- $\alpha$ , which is critical in the pathogenesis of severe acute pancreatitis, including pancreatic and peri-pancreatic necrosis, systemic inflammatory response syndrome and persistent organ failure. In experimental acute pancreatitis animal models, serum TNF- $\alpha$  activity increases within three hours of the induction of acute pancreatitis and its serum level is significantly higher in severe disease compared to mild disease. TNF- $\alpha$  activity can be blocked by mono-clonal or poly-clonal antibodies and the synthesis of TNF- $\alpha$  can be blocked by pentoxifylline, a nonselective phosphodiesterase inhibitor. In a recent double-blinded randomized control pilot trial, pentoxifylline decreased the necessity of ICU admissions, and shortened ICU stays and prolonged hospitalization time (more than 4 days).<sup>16</sup> It is an oral medication that can be safely and easily given to all patients without

Drug therapy for acute pancreatitis is actively under investigation and future understanding of the disease pathophysiology and better designed trials are needed to make significant advances in the management of this disease.

the need to predict the severity of the acute pancreatitis. Despite the theoretical increased risk of infectious complications, no adverse effects were noted in the patients receiving pentoxifylline in the pilot trial. Pentoxifylline may also have independent benefits besides blocking TNF- $\alpha$ , like effects on rheology and renal protection. NIH has recently funded a larger, randomized controlled study to further confirm the promising results.

The discrepancy between animal studies

and human clinical trials can be explained by many things, including flaws in clinical trial designs, inadequate dosages of medication and suboptimal drug delivery (timing and route). In addition, the reliability of the acute pancreatitis animal model in human disease is also unclear.

In summary, at the present time specific drug therapy for acute pancreatitis is actively under investigation and future understanding of the disease pathophysiology and better designed, randomized clinical trials are needed to make significant advances. Significant improvement in acute pancreatitis animal models or modern technology for *in vitro* human pancreas culturing system are crucial to better understanding the pathophysiology. At the present time, a reliable method to predict the moderately severe and severe types of acute pancreatitis is not available. Hence, the ideal drug to treat acute pancreatitis should be safe, cheap and easily administered to all patients in any clinical setting. ■

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## Chemoprevention for Colon Cancer

# DREAM OR REALITY?

Wouldn't it be nice to take a pill or dietary supplement and prevent colorectal cancer (CRC)? This is easier said than done, but we are making progress.



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**C**RC is the second leading cause of cancer death in industrialized nations, accounting for 10 percent of the total cancer burden with an individual lifetime risk of approximately 6 percent in the U.S. While the highest impact form of prevention is CRC screening, the development of effective, inexpensive and safe chemopreventive agents would be of great benefit. Chemoprevention of colon cancer through the use of agents to prevent or suppress the progression of precursor lesions is a concept that is finding growing acceptance. Initial enthusiasm was based on epidemiology, animal trials, small clinical trials using biomarkers and trials in high-risk groups. The results of prospective, randomized trials relevant to the general (average-risk) population have in many cases been less impressive or definitive, but a number of recent trials have provided evidence that chemoprevention of colorectal neoplasia may become a reality. What is acceptable in

terms of safety will depend on the risk for cancer development in a given population, the magnitude of risk reduction (preferably measured in reduced mortality) and the toxicity of a given agent.

For chemoprevention to become a reality, we need not only an effective agent, but one which can be used safely for long periods of time in healthy people. Minimal or no toxicity is acceptable when an agent is used in a population at average risk of colon cancer; it is a matter of balancing benefit versus risk. This lesson was learned when it was proposed that cyclooxygenase-2 (COX-2) inhibitors would make ideal agents for chemoprevention of CRC. After all, these agents had proved to have less GI toxicity than standard NSAIDs. Given biological plausibility, preclinical *in vitro* and animal data, and data on the regression of adenoma in patients with familial adenomatous polyposis, three randomized trials were undertaken to examine the effect of COX-2

selective inhibitors on formation of new adenomas in patients with a history of sporadic adenomas. While these studies demonstrated significant reductions in new adenoma formation associated with use of these agents (up to 66 percent reduction in the number of patients developing advanced adenomas), they were also associated with a two-fold increased risk of cardiovascular events, such as myocardial infarctions and stroke. This increased cardiovascular risk led to one of the largest drug recalls in history.

Dietary chemoprevention has a strong appeal. There is convincing evidence that lifestyle and dietary risk factors are associated with increased or decreased risk of colon cancer, and the lay public does not often consider dietary supplements as taking a “drug.” Unfortunately the scientific evidence for dietary chemoprevention seems “softer” than for other preventable causes of disease. Where epidemiologic evidence often seems strong, randomized clinical trials have been disappointing. High-fiber diets are associated with a reduced incidence of CRC in many epidemiologic studies, yet well-designed randomized trials have been negative. Folate has been protective against CRC in epidemiologic and preclinical trials, yet a large prospective randomized trial failed to demonstrate a protective effect of folate supplementation on recurrence of adenoma compared with placebo. It also suggested that folate supplementation in people with prior adenomas actually might increase adenoma risk. Even the protective effect of calcium has recently been called into question. These results do not mean that these agents are not protective, but point out the difficulty in carrying out and interpreting such studies. Nutritional epidemiology benefits from precision of measurement but there are often confounding variables and interactions, while intervention trials take place in a limited window and are often unable to examine dose-response.

All, however, is not doom and gloom. The most promising results and lessons for CRC

prevention and risk versus benefit come from trials using aspirin. Case-control and cohort studies suggest that the risk for adenoma and carcinoma may be reduced 40 to 50 percent among long-term aspirin users compared with controls. In four large randomized trials of aspirin used for primary and secondary prevention of cardiovascular disease (a benefit of aspirin), aspirin reduced the 20-year risk of colon cancer by 24 percent and mortality by 35 percent. At least four prospective adenoma prevention trials now provide compelling evidence that aspirin use reduces the risk of colorectal adenoma in people with a history of adenoma or carcinoma. Molecular epidemiology in aspirin users has also taught us that preventive agents interact with genetic variation, and are not equally effective across the population. Regular use of aspirin appears to reduce the risk of

## It is the question of benefit versus risk that remains to be answered.

colon cancers that express COX-2, but not the risk of those with weak or absent COX-2 expression. Likewise, CRC survival appears to be increased in aspirin users whose tumors contain PI3 kinase mutations but not in those without mutations. Thus, molecular epidemiology might be used to improve benefit versus risk. Despite this compelling data it is unclear what the benefit to risk is for long-term aspirin use in low-cancer-risk populations, and what the optimal aspirin dose (81 mg versus 325 mg) should be. Aspirin is associated with a two-to-six-fold increase in GI bleeding and intracranial hemorrhage, but complications of aspirin occur early and may be over-attributed (half of the bleeds may have occurred without aspirin).

So are we making progress? I would argue that the answer is yes. Clearly, effective agents for chemoprevention of colon cancer exist.

Proof of principle has evolved to proof in this regard. It is the question of benefit versus risk that remains to be answered. I would submit that we can, even now, tailor use of a given agent based on the ratio of benefit to risk. We might choose to use aspirin, for example, in those with a history of colon cancer, advanced or recurrent adenoma or a family history of CRC, especially in those with high cardiovascular risk (reduced by aspirin) and low GI bleeding risk. The U.S. Preventive Services Task Force (USPSTF) is now considering recommending the use of low-dose aspirin for primary prevention of cardiovascular diseases and colorectal cancer in adults 50 to 59 years who have a 10 percent or greater 10-year cardiovascular disease risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin for at least 10 years. Consideration of the risk to benefit ratio for other age groups is emphasized in a draft statement from the USPSTF. Studies of cardiovascular risk associated with COX-2 inhibition have also demonstrated who is at high- or low-risk for complications associated with an otherwise effective chemoprevention agent. We also need to look forward to other agents and combinations of agents (a large trial of aspirin and n-3 polyunsaturated fatty acids derived from fish oil is currently underway in the United Kingdom), revisit nutritional prevention and reduce risk factors for CRC that we can control such as obesity, lack of physical activity and tobacco use.

Will chemoprevention replace colon cancer screening? Almost assuredly not. Successful chemoprevention, however, could supplement the benefit of screening by targeting missed lesions, addressing the development of interval lesions, decreasing the number of adenomas that need to be removed at future colonoscopy, and slowing the growth of early cancers. ■

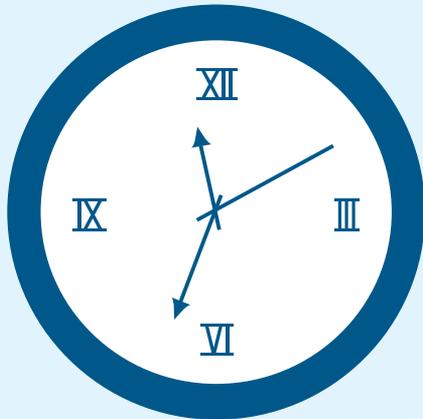
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