Experts debate whether or not we should train non-physicians to do endoscopy.

ARTICLES BY

Louis Korman, MD, and Lukejohn Day, MD
Note From the Editor

Welcome to the December/January issue of AGA Perspectives. This issue starts with a point-counterpoint on the role of physician extenders in GI endoscopy. This controversial issue is debated by Dr. Lukejohn Day who argues that there are many benefits of this approach and Dr. Louis Korman who suggests “not so fast!” I think you will find both sides of this debate provocative.

This issue also updates the readership on a host of evolving concepts in hepatology today. Drs. Ruben Hernaez and Hashem B. El-Serag provide an update on hepatocellular carcinoma, Drs. Chatur Acharya and Jasmohan S. Bajaj discuss the role of the microbiome—gut—liver—brain axis in hepatic encephalopathy and the HCV Care Pathway is presented by the AGA Institute.

Moving away from the liver, one of the most exciting new procedures in gastroenterology today is peroral endoscopic myotomy (POEM), a topic that was recently addressed in an AGA Clinical Practice update. Dr. Mouen A. Khashab, who has extensive experience with this technique, provides his perspective of the role of POEM in achalasia and gastroparesis.

This issue concludes with a primer from the AGA Education and Training Committee on maintenance of certification (MOC), a topic of importance for all gastroenterologists, notwithstanding all the concerns raised about the MOC process.

I hope you enjoy this issue of AGA Perspectives and I want to take the occasion to wish you all a happy and healthy new year.

Best,

Gary W. Falk, MD, MS, AGAF
Editor
@DrGaryFalk
Over the last 30 years there has been a dramatic rise in the demand for endoscopic procedures across the world and in the United States. This rising demand is for both colorectal cancer (CRC) screening and diagnostic procedures. At the same time, there has not been a corresponding increase in the number of providers who can perform these procedures. For example, the number of gastroenterologists being trained has remained steady in the U.S. and is expected to remain unchanged for the next several years. Consequently, there is a growing gap between the demand for and capacity to provide endoscopic procedures as well as an inability to meet the growing need for CRC screening. Therefore, the health care community is required to develop innovative solutions to help address this gap. One such innovative solution is the use of non-physicians to perform endoscopic procedures.

Several questions arise on the topic of non-physicians performing endoscopy. First, can non-physicians safely and adequately perform endoscopy? The use of non-physicians to provide clinical services is widespread. Mid-level providers can act both independently without supervision, i.e. nurse practitioner, or act as surgical assistants, i.e. physicians assistants.

First, which procedures are we considering for non-physicians: sigmoidoscopy, upper endoscopy, colonoscopy, ERCP or endoscopic ultrasound? Second, within those procedures, are we considering training in diagnostic or therapeutic procedures? One could debate each of these points but because of space limitations I would like to restrict this discussion to screening colonoscopy.

In the United States, we should not train non-physicians to perform colonoscopy. The reasons for this position are the following:

1. We don't need more endoscopists to perform colonoscopy as part of our colorectal cancer (CRC) prevention program.
Patients report high satisfaction with respect to non-physicians performing flexible sigmoidoscopy, colonoscopy, and upper endoscopy, and in many cases, there is greater patient satisfaction and lower pain scores with non-physicians performing endoscopy.

CSC screening by colonoscopy is a significant financial burden on the health care system. However, it is not clear that using less expensive providers will reduce the cost significantly. Costs vary greatly depending on the professional location of care and hospital versus ambulatory surgery settings, availability of services and insurance coverage. Thus, major variances in cost are not solely based on the relative cost of physicians versus non-physicians performing the procedure. In fact, the physician fee may account for as little as 20 percent of the total cost. Medicare data for 2007 published by the U.S. Department of Health and Human Services Digestive Health Network Inc. calculated that $414.5 million was spent for colonoscopy, indicating a total program cost for outpatient colonoscopy of $1.88 billion. Costs including facility, pathology, anesthesia, and monitoring and assuring the performance of the non-physician endoscopist are not widely used to replace trained physicians. 2. We will not save money by using non-

simple endoscopic procedures. Available data with regards to patient satisfaction is sparse and varied in this area; however, limited reports illustrate that patients would be willing to undergo a repeat procedure by a non-physician with respect to non-physicians and physicians in terms of patient preference for who performs the procedure. Patients report high satisfaction with respect to non-physicians performing flexible sigmoidoscopy, colonoscopy, and upper endoscopy, and in many cases, there is greater patient satisfaction and lower pain scores with non-physicians performing endoscopy. Lastly, the use of non-physicians in traditionally physician roles is not a new concept. Several medical fields have adopted the use of non-physicians for clinical practice. For example, the use of certified nurse anesthetists to deliver anesthesia care has been prevalent for over a century. Nurse anesthetists have consistently demonstrated efficacy and safety with high provider satisfaction and acceptance. Consequently, expanding the role of non-physicians into endoscopy would not limit the role of gastroenterologists, but rather permit them to increase services and access, and further allow gastroenterologists to focus their attention on more complex and demanding procedures/cases.

Finally, there is a need for non-physicians to perform endoscopic procedures in the U.S. One of the largest demands for endoscopic care is based on indications for colorectal cancer screening and surveillance, which require over 14 million colonoscopies and nearly three million flexible sigmoidoscopies are performed annually just for CRC screening and it has been projected that gastroenterologists alone will not be able to meet this demand. Both colonoscopy and upper endoscopy are accepted and recommended modalities for colorectal cancer screening, yet with the aging population, it is estimated that a significant number of endoscopic procedures that need to be performed to meet this demand for exceeds the supply of available gastroenterologists. This imbalance will vary from impaired access, delayed diagnoses, higher health care costs and overall poorer patient satisfaction. Non-physicians are a suitable and safe adjunct to physicians performing simple endoscopic procedures to meet this rising demand.

The rapidly occurring changes in the U.S. health care system will have a tremendous impact on non-physicians performing endoscopy. As more Americans have improved access to health care, we will likely see a continued increase in the number of endoscopic procedures. Non-physicians have been performing high quality and safe endoscopic procedures since the 1970s, with the first procedure performed being flexible sigmoidoscopy. In recent years, this practice has expanded. Non-physicians have begun to perform colonoscopy and upper endoscopy, although in more limited health care settings. Aplae evidence exists that non-physicians can safely perform endoscopic procedures with similar quality, especially with respect to screening flexible sigmoidoscopy, colonoscopy and diagnostic upper endoscopy. In fact, in some cases non-physicians can outperform physicians with regards to several important quality indicators in endoscopy. Additionally, in many cases the expansion of non-physicians performing endoscopy has occurred in resource-limited settings with vulnerable patient populations. It is not clear that non-physicians could become the primary care provider for colorectal cancer screening and surveillance. In fact, large scale studies have demonstrated that no difference exists between procedures that need to be performed to meet this demand for exceeds the supply of available gastroenterologists. This imbalance will vary from impaired access, delayed diagnoses, higher health care costs and overall poorer patient satisfaction. Non-physicians are a suitable and safe adjunct to physicians performing simple endoscopic procedures to meet this rising demand.

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QUICK HITS: PATIENT CARE

WHAT'S ON THE HORIZON?

STAYCOURSE

Hepatocellular Carcinoma (HCC)

What’s On The Horizon?

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Epidemiology. Recent data from the U.S. Cancer Statistics registry show that hepatocellular carcinoma (HCC) continues to rise albeit at a slower rate recently (4.5 percent increase annually from 2000 to 2009, and 0.7 percent from 2010 to 2012). Men between 55 and 64 years of age, Hispanics and, at state-level, Texans, are the most commonly affected groups. Hepatitis C infection (HCV) is still the most common underlying etiological risk factor of HCC including those waitlisted for liver transplant. New and highly potent direct-antiviral agents (DAAs) are expected to decrease the risk of HCV-related HCC depending on the extent to which these medications are used in the population. Sustained virological response (SVR) considerably reduces HCC and complications of portal hypertension, but does not eliminate the risk or need for surveillance in the presence of advanced fibrosis or cirrhosis. Metabolic syndrome with or without non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of HCC, even in the absence of cirrhosis. NAFLD/non-alcoholic steatohepatitis (NASH) related HCC seems to account for close to 10 percent of HCC in the United States; however, given the high prevalence of metabolic syndrome in the general population, there is a considerable potential for another epidemic of HCC.

HCC surveillance. American and European guidelines recommend ultrasound with or without alpha-fetoprotein (AFP) as surveillance tools for HCC; however, contrast-enhanced ultrasonography and magnetic resonance imaging (MRI) are being tested. In many transplant facilities across the United States, MRI is the preferred surveillance imaging technique as it has shown higher sensitivity and specificity to detect biopsy and explant-proven HCC compared to ultrasound or CT. Recently, Kim et al. in South Korea performed a prospective cohort study of 487 cirrhotic patients with 1,100 HCC surveillance episodes with paired ultrasonography and MRI, and found that the HCC detection rate of MRI was 86 percent, significantly higher than the 27.9 percent of ultrasound. Ultrasonography also had higher false-positive rate findings than MRI (5.6 percent vs. 3 percent, P = .004). Is MRI ready for HCC population-based surveillance? Probably not, as it takes longer and costs more than conventional abdominal ultrasound; however, recent data suggests that an abbreviated MRI protocol — utilizing only dynamic contrast-enhanced images compared to a conventional liver MRI — can be accurate for the characterization of observations in at-risk patients. Excellent agreement was found between the abbreviated T1-only MRI protocol and a full liver MRI, with only 5 percent of cases changing radiological categorization with only seven to 10 minutes duration. While an area of active research, there have been no new biomarkers. Three biomarkers — AFP, AFP-L3 and des-gamma-carboxy prothrombin (DCP) — either alone or in combination with age and alanine aminotransferase (ALT), increase the sensitivity of detecting HCC during surveillance but are also associated with an increase in the false positive tests. Similarly, calculators combining AFP with demographic risk (age) and clinical (ALT and platelets levels) are being developed to improve AFP performance.

Treatment. Several staging systems can be applied including the Barcelona Clinic Liver Cancer staging system or the Hong Kong Liver Cancer staging system, and whereas none are perfect, they guide clinicians to treat each stage. Early stage small HCC can be managed with percutaneous ablation, resection or transplant with similar long-term outcomes. In those with more advanced stages, best survival and recurrence-free survival are obtained with transplantation following strict selection protocols (e.g. Milan criteria). Novel techniques in ablation, such as laser and cryosublation, have shown promising results, associated with less local side effects than microwave or radiofrequency ablation. Palliative therapies, such as arterially directed therapies, continue to be used either as end-therapy or, sometimes, as a bridge to transplantation. Radioembolization with Yttrium-90 microspheres is becoming more widely available with good results in otherwise unresectable tumors (e.g. vascular invasion), and with the advantage of being performed in an outpatient setting. The treatment of advanced HCC has seen some advancements. Regorafenib is a new oral multi-kinase inhibitor that has shown some benefit in those patients who progress while on sorafenib, adding approximately two months median survival time. Combining sorafenib with other therapies including resection, ablation or transarterial chemoembolization (TACE) is not useful. In 2017, FDA approved a supplemental new drug application for lenvinitib, an oral multikinase receptor tyrosine, as a frontline systemic treatment for patients with advanced HCC. A median survival of 13.2 months was shown in a Phase III randomized non-inferiority trial of lenvinitib vs. sorafenib. Further results from immune checkpoint inhibitors such as nivolumab, tremelimumab and ipilimumab, are expected in the near future. In summary, HCC continues to be an important public health problem — likely as a result of a baby-boomer HCC-related cirrhosis — and while we expect some plateau or decrease of the HCV-related HCC, attaining DAA related SVR reduces but does not eliminate HCC in patients with cirrhosis. Future directions will likely show improvement on surveillance techniques (including MRI) and treatment options of incurable HCC with new oral agents.

REFERENCES
The positive outcomes of esophageal POEM have resulted in a new application of the procedure (performed in the stomach) for the treatment of some patients with gastroparesis with symptoms refractory to dietary and medical therapy. These early results suggest that G-POEM may play a role in a subset of patients with gastroparesis. It is believed that gastroparetic patients with pylorospasm will be most appropriately for G-POEM and, as such, the most pressing current need is the accurate identification of such patients. Emerging data on the role of impedance planimetry using Fliip9 (functional luminal imaging probe) (Crippson, Ireland) suggests its potential in the identification of a distinct subset of patients with decreased pyloric distensibility. Whether this information will lead to more tailored therapy and selection of a clinical subset that may more readily benefit from G-POEM remains to be seen and further investigation is ongoing.

**REFERENCES**


The gut-brain axis is a relatively new focus of research that has rapidly expanded after the development of culture-independent analytic techniques. Of interest to hepatologists is the microbiome-gut-liver-brain axis and its role in the pathogenesis of hepatic encephalopathy (HE). HE is defined as brain dysfunction secondary to liver transaminitis and/or portosystemic shunts, which is epidemic in cirrhosis and is the leading cause of readmissions in North American cirrhotic patients. It has two major subtypes, covert (CHE), which is subclinical, and overt (OHE), the clinically apparent form. Fundamental to the pathogenesis in both subtypes is gut microbial dysbiosis, which is a deleterious shift in microbial community composition. This means a higher relative abundance of potentially pathogenic taxa that are predominantly gram-negative bacteria that produce endotoxins and generate a pro-inflammatory milieu which engages the host immune system.

Each cirrhosis etiology, such as alcohol or non-alcoholic fatty liver disease, has a specific gut microbial fingerprint i.e dysbiotic features. Regardless of etiology, decompensation of cirrhosis and HE development is associated with a worsening of dysbiosis compared to the compensated and non-cirrhotic stage. Microbiota can potentiate HE through several potential pathways related to endotoxemia and ultimately, an altered microbiome-gut-liver-brain axis is critical in the development and propagation of hepatic encephalopathy and there remains a need for targeted therapies to modulate this connection between the gut and the brain.

Ultimately, an altered microbiome-gut-liver-brain axis is critical in the development and propagation of hepatic encephalopathy and there remains a need for targeted therapies to modulate this connection between the gut and the brain.

The future of HE treatment lies in targeted therapies; more specifically gut targeted specific options. In a small randomized clinical trial, fecal microbial transplantation (FMT) via lower-intestinal delivery was useful but larger randomized studies are required. FMT changes the gut microbiota composition and can improve microbial function to potentially improve brain function. Genetically engineered bacteria that can consume ammonia are also in the process of being studied. Newer therapies will also need to be studied as additives to current treatments for HE given the limited success of the drugs currently recommended. In addition, there is no consensus or multi-center randomized trials for CHE therapy. Ultimately, an altered microbiome-gut-liver-brain axis in critical in the development and propagation of HE and there remains a need for targeted therapies to modulate this connection between the gut and the brain.

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HCV CARE PATHWAY

A Report from the AGA Institute HCV Care Pathway Work Group

Members of the work group: Fasiha Kanwal, Bruce R. Bacon, Lauran A. Beste, Joel V. Brill, Allen L. Gifford, Stuart C. Gordon, Michael A. Horberg, Jacob G. Manthey, Nancy Reau, Vinod K. Rustgi and Zobair M. Younossi

Approximately 50 percent of Americans with chronic hepatitis C virus (HCV) are unaware of their infection status and far fewer have received curative antiviral therapy. New direct-acting antiviral (DAA) treatments offer an unprecedented opportunity to cure the more than 2.7 million individuals in the U.S. affected with HCV. Once HCV infection is recognized, linkage-to-care interventions are important to ensure that patients are afforded access to antiviral treatment.

By implementing the AGA HCV Care Pathway in practice settings, clinicians and health care systems will be able to provide care that is consistent with evidence-based guidelines and performance measures, leading to value-based, efficient, safe and effective care. Given the diversity in health care delivery systems across the world, this pathway may not be generalizable to patients and systems across the world, this pathway is recommended for all persons born between 1945-1965, and for anyone with transmission risk factors (e.g., history of injection drug use, transfusion or organ transplant before 1992, received clotting factor before 1987, history of long-term dialysis, HIV infection, percutaneous exposure to HCV-infected blood, or mucosal exposure to HCV-positive blood, and children born to HCV-positive women).

One-time screening for at-risk patients has been shown to be effective, so it’s important to screen patients where they are at both the outpatient and inpatient settings. As a covered service under the Affordable Care Act, HCV testing is available without financial responsibility to insured patients born between 1945-1965, and for anyone with risk factors before 1987, history of long-term dialysis, HIV infection, percutaneous exposure to HCV-infected blood, or mucosal exposure to HCV-positive blood, and children born to HCV-positive women.

Organization of HCV Care Team

Integrated multidisciplinary care has proven effective in improving HCV treatment and sustained virologic response (SVR). Practices will vary in their HCV care workflows, and thus the capacities of individual practices to dedicate staff to each role will likely vary. The clinical team may include:

- Care coordinator — main point of contact for the patient throughout all aspects of treatment and care; may be done by a nurse, social worker, health technician or another appropriate team member.
- Clinical pharmacist — administers pre-treatment assessment for drug interactions, monitors adherence, preventative waste and diversion of expensive medications.
- HCV specialist — provides pre-treatment evaluation and prescribes HCV treatment; may be trained in hepatology, gastroenterology or infectious diseases, but in some cases with appropriate training and support, could be a general internist, or other primary care provider.
- Mental/substance abuse provider

Initial Evaluation of Patients With HCV

The first visit is an opportunity to assess medical conditions that may contribute to progression, risk of complications or potential treatment regimens. Although HCV eradication is considered beneficial in virtually all infected persons, a patient must be physically and mentally ready for treatment. Continued patient education and obtaining follow-up data for conditions identified at the first assessment should be the objectives for the second visit. This visit also offers an opportunity to initiate treatment or treatment planning.

Post-Treatment Monitoring and Follow-Up Care

Appropriate follow-up recommendations and ongoing linkage to liver-related care is important for excellent HCV care. Patients who do not achieve SVR after antiviral treatment should continue to receive ongoing monitoring for progressive liver fibrosis. At this point, patients may be referred to an experienced HCV provider, preferably one with access to clinical trials for patients who did not respond to the current DAsa.

More detailed information can be found in the full HCV Clinical Pathway in Gastroenterology (gastrojournal.org).

Quick Hits: Patient Care

More needs to be done to reach a variety of populations infected with chronic HCV [Figure 1] HCV screening is recommended for all persons born between 1945-1965, and for anyone with transmission risk factors (e.g., history of injection drug use, transfusion or organ transplant before 1992, received clotting factors before 1987, history of long-term dialysis, HIV infection, percutaneous exposure to HCV-infected blood, or mucosal exposure to HCV-positive blood, and children born to HCV-positive women).

Outreach and Screening

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Everything You Need To Know About MOC

AGA has called on the American Board of Internal Medicine (ABIM) to make changes to their recertification pathway to meet the needs of practicing GIs. We’re pleased that ABIM has listened to our concerns and instituted changes to the program, but we recognize there may be some confusion about what’s expected of you. As we enter 2018, the AGA Education and Training Committee would like to provide you with 10 helpful tips on obtaining and better understanding maintenance of certification (MOC) requirements, and 10 things to know about the new two-year knowledge check-in. AGA will continue to advocate for a recertification pathway that reduces the burden of recertifying, emphasizes learning over testing and assesses diplomates in their areas of practice.

10 Things — MOC Edition

1. MOC compliance applies only to those who were initially certified on or after 1990. The American Board of Internal Medicine (ABIM) "strongly urges" those certified prior to 1990 to participate in MOC but they will not lose their board certification status for not participating. For all diplomates, ABIM will report if they are or are not participating in the MOC program.

2. Every two years, a diplomate must complete at least one MOC activity. It does not matter what the activity is nor how many points it is worth, there just needs to be some accumulation of a MOC point(s) once every two calendar years. If this two-year requirement is not met, the diplomate will be reported as "not participating in MOC." 

3. Every five years, a diplomate must earn 100 MOC points. This is required to stay certified.

4. Wondering where you are in this two-year/five-year cycle? The best way to check is to log in to myMOC on the ABIM website (www.abim.org).

5. The Knowledge Check-In will be offered four to six times a year. It is a shorter test. It is anticipated to take most diplomates two and a half to three hours to complete.

6. The Knowledge Check-In will only be offered every other year.

7. Results will be given immediately following the test-takers completion of the Knowledge Check-In.

8. The first year an exam is offered in a specialty, test-takers completion of the Knowledge Check-In will cover all the certifications a diplomate is maintaining.

9. A diplomate’s 10-year exam is due in 2019, he or she can choose to take the traditional 10-year Long Format Exam, or to engage in the new two-year Knowledge Check-In.

10. Confused? More information is available from AGA’s website (www.abim.org) or a testing center.

10 Things — Two-Year Knowledge Check-In Edition

1. Beginning in 2019, gastroenterology diplomates have the option to choose a two-year Knowledge Check-In in place of the 10-year Long Form Exam.

2. Those recertifying in transplant hepatology will not have a two-year option until 2020.

3. The Knowledge Check-In is taken at home, work or a testing center.

4. It is a shorter test. It is anticipated to take most diplomates two and a half to three hours to complete.

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6. The Knowledge Check-In will only be offered every other year.

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Gastroenterologists

The Division of Gastroenterology and Inborn Errors Products at the US Food and Drug administration is seeking Gastroenterologists to join our team. The physician will participate in all aspects of the drug development process. Specific responsibilities include evaluation of safety and efficacy data submitted with new drug applications, providing guidance to industry sponsors on all aspects of drug development including trial design, endpoints, selection of appropriate patient populations, providing guidance on pediatric drug development plans, conducting independent assessment of safety signals in the pre and post-approval setting, and education/outreach to the GI community. The ideal candidate is a physician who is board eligible or board certified in Gastroenterology or Pediatric Gastroenterology, has strong technical writing and critical thinking skills, and an interest in learning regulatory science. Experience in clinical trials design and/or conduct is beneficial, but not required. This is an excellent opportunity for a physician with a strong interest in the science of Gastroenterology, who is seeking a career path where Gastroenterology skills and expertise will be utilized every day to have a broad impact on the health of GI patients.

All questions regarding the position, benefits, and salary may be directed to the OND Recruitment Team at ond-employment@fda.hhs.gov or (301) 796-0800. To apply, please submit a cover letter and CV/resume to ond-employment@fda.hhs.gov. Please indicate that you are applying to source code #018-001EG.

Applicants must have a Doctor of Medicine or Doctor of Osteopathy degree from an accredited medical school. Graduates of foreign medical schools must be certified by the Education Commission for Foreign Medical Graduates (ECFMG). Applicants must have a permanent, full, and unrestricted license to practice medicine in a State, District of Columbia, or a territory of the United States. Candidates for Civil Service or U.S. Commissioned Corps must be U.S. citizens. Permanent U.S. residents may apply for staff fellowship appointments.

Classifieds

WASHINGTON, DC

Gastroenterologists

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Upcoming Research Funding Opportunities

The AGA Research Foundation is pleased to offer travel awards for investigators presenting at Digestive Disease Week® 2018.

APPLICATIONS DUE FEB. 16, 2018

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Sofosbuvir-based therapy changed expectations in HCV treatment, providing the chance for a cure to a broad range of patients.

INDICATIONS

**HARVONI** is indicated for the treatment of adults with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis. HARVONI is used with ribavirin in GT 1 adults with decompensated cirrhosis and in GT 1 or 4 adult liver transplant recipients without cirrhosis or with compensated cirrhosis.

**EPCLUSA** is indicated for the treatment of adults with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis and in combination with ribavirin for those with decompensated cirrhosis.

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

**BOXED WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN HCV/HBV COINFECTED PATIENTS**

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with HARVONI or EPCLUSA. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals (DAAs) and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive, in patients with serologic evidence of resolved HBV, and also in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV DAAs may be increased in patients taking these other agents. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA, including BOXED WARNING, on the following pages.
HARVONI: AN ESTABLISHED SINGLE-TABLET REGIMEN FOR YOUR GT 1 PATIENTS

OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS 1,4-6
(n=1042/1079; ION-1, -2, -3)

97%

HARVONI demonstrated a favorable safety profile with low rates of 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 (ION-1, -3, ION-1, and ION-2):
  - fatigue (13%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%)

HARVONI Clinical Study Designs: randomized, open-label trials in GT 1 subjects

ION-1: TN subjects (N=1065) without cirrhosis or with compensated cirrhosis received HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

ION-2: TE subjects (N=440) without cirrhosis or with compensated cirrhosis received HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

These studies did not include subjects who were liver transplant recipients and/or with decompensated cirrhosis.

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

CONTRAINDICATIONS

- If HARVONI or EPCLUSA 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

- Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Amiodarone is not recommended for use with HARVONI or EPCLUSA 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. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir containing regimen. 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 Due to Use with P-gp Inducers and/or Moderate to Potent Inducers of CYP: Rifampin, St-John’s wort and carbamazepine are not recommended for use with HARVONI or with EPCLUSA. P-gp inducers may significantly decrease ledipasvir, sofosbuvir and/or velpatasvir plasma concentrations. Moderate to potent inducers of CYP2C8, CYP2C19 or CYP3A4 may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.

OVERALL CURE RATE IN GT 1-6 SUBJECTS 1,4-6
(cott/1035; ASTRAL-1, -2, -3)

98%

EPCLUSA demonstrated a favorable safety profile with low rates of AEs across clinical trials:

- Adverse reactions (all grades) reported in ≥5% of subjects receiving 12 weeks of treatment with EPCLUSA (ASTRAL-1): headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%).

- The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1:

  - In ASTRAL-3, irritability was observed in ≥5% of subjects treated with EPCLUSA.

  - EPCLUSA Study Designs: randomized trials in TN and TE subjects without cirrhosis or with compensated cirrhosis

ASTRAL-1: Double-blind, placebo-controlled trial in GT 1, 2, 4, 5, or 6 subjects (N=1040). GT 1, 2, 4, or 6 subjects were randomized to receive EPCLUSA or placebo for 12 weeks. GT 5 subjects received EPCLUSA for 12 weeks. Overall SVR was 99% (n=918/934).

ASTRAL-2: Open-label trial in GT 2 subjects (N=266). Subjects received EPCLUSA or SOF + RBV for 12 weeks.

ASTRAL-3: Open-label trial in GT 3 subjects (N=552). Subjects received EPCLUSA for 12 weeks or SOF + RBV for 24 weeks. SVR2 for EPCLUSA ranged from 99% (TN with compensated cirrhosis) to 95% (TN without cirrhosis).

These studies did not include subjects with decompensated cirrhosis (Child-Pugh C).

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

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

ADVERSE REACTIONS

- The most common adverse reactions (≥10%), all grades) with HARVONI were fatigue, headache, and asthenia.

- The most common adverse reactions (≥10%, all grades) with EPCLUSA were headache and fatigue; and when used with RBV in decompensated cirrhotics were fatigue, anemia, nausea, headache, insomnia, and diarrhea.

DRUG INTERACTIONS

- HARVONI: Coadministration is not recommended with omeprazole, pirenidone, pranlukast, rosuvastatin, or erlotinib due to decreased concentrations of ledipasvir and sofosbuvir, or with imatinib (ciprofloxacin/colchicine/trimetrexate) due to increased concentrations of foscarnet or with mycophenolate mofetil due to increased concentrations of mycophenolic acid. When used with RBV in decompensated cirrhotics, or with erlotinib due to decreased concentrations of fosfomycin and/or velpatasvir.

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

Learn more at hcp.harvoni.com and hcp.epclusa.com

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA, including BOXED WARNING, on the following pages.
If HARVONI is acting antivirals (DAAs) and were not receiving HBV antiviral therapy. Pregnancy avoidance, apply to this combination regimen. Refer to RBV prescribing information. If HARVONI is administered with RBV, the contraindications to RBV also apply to this combination regimen. Refer to RBV prescribing information.

**CONTRAINDICATIONS**

HARVONI is contraindicated in patients with known hepatitis B virus (HBV) infection before initiating treatment with HARVONI. HBV reactivation has been reported in HBV coinfected patients who were under treatment with an HIVdirect acting antivirals (DAAs) and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Conversely, concomitant hepatocellular carcinoma, which is not recommended.

**INDICATIONS AND USAGE**

HARVONI is indicated for the treatment of patients 12 years of age and older who are infected with HCV GT 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh Class A or B) and have not had prior or failed prior antiviral therapy. Patients with advanced liver disease may be at increased risk for symptomatic bradycardia because of coadministration with RBV. There have been isolated, asymptomatic cases of increased ledipasvir and simeprevir exposures across HCV GT 1, 4, 5, and 6 infection in adults. Safety and efficacy of HARVONI were assessed in two Phase 2, open-label trials of 100 subjects 12 years of age and over (9% of total number of subjects in the clinical studies). No overall differences in safety were observed between male and female patients. However, because women are generally at a higher risk of developing myopathy, myalgia, and bone fracture, the potential for an increased risk of such adverse events in women should be considered when evaluating the benefits and risks of treatment with HARVONI in women of childbearing potential.

**ADVERSE REACTIONS**

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

**Summary (cont.)**


**REFERENCES**

1. Antiviral Drugs for Treatment. May 2016.
5. Lactation: Consider alternative HCV or antiretroviral therapy to prevent breastfeeding. The development and health benefits of human milk have been established. However, there is no information about its effects on the breastfed child. Use of HARVONI by a woman who is or may become pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. The risk of transmission of HCV through breastfeeding is not known. Consider alternative HCV or antiretroviral therapy to prevent breastfeeding. There is no information about the effects of HARVONI on male fertility. Lactation: No data are available to establish whether or not HARVONI poses a risk to pregnancy. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. It is not known whether the components of HARVONI or their metabolites are present in human breast milk (lactate). Harmful effects are possible for a breastfed infant. Because of the potential for serious adverse reactions in nursing infants and the lack of information on the effects of HARVONI on human milk, the decision to use this medication in a nursing mother should be made with consideration of the importance of the drug to the mother. Use of HARVONI by a woman who is or may become pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. The risk of transmission of HCV through breastfeeding is not known. Consider alternative HCV or antiretroviral therapy to prevent breastfeeding. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. There is no information about the effects of HARVONI on male fertility. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. The risk of transmission of HCV through breastfeeding is not known. Consider alternative HCV or antiretroviral therapy to prevent breastfeeding. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. The risk of transmission of HCV through breastfeeding is not known. Consider alternative HCV or antiretroviral therapy to prevent breastfeeding. The risk of transmission of HCV through breastfeeding is not known. Consider alternative HCV or antiretroviral therapy to prevent breastfeeding. Because of the potential for serious adverse reactions in nursing infants and the lack of information on the effects of HARVONI on human milk, the decision to use this medication in a nursing mother should be made with consideration of the importance of the drug to the mother. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. The risk of transmission of HCV through breastfeeding is not known. Consider alternative HCV or antiretroviral therapy to prevent breastfeeding. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. Use of HARVONI by a woman who is pregnant should be based on the known benefits of the drug to the patient and any potential risk to the fetus. Because of the potential for serious adverse reactions in nursing infants and the lack of information on the effects of HARVONI on human milk, the decision to use this medication in a nursing mother should be made with consideration of the importance of the drug to the mother.
In ASTRAL-1, isolated, or self-monitoring of the heart rate should occur on a daily basis through coadministration with a sofosbuvir-containing regimen. A fatal cardiac arrest Amiodarone: reactivation during HCV treatment with EPCLUSA and during posttreatment treatment with HCV direct-acting antivirals may be increased in these patients. resulted in fulminant hepatitis, hepatic failure, and death. Some cases have been reported in fulminant hepatitis, heart failure, and death. Most were asymptomatic or with no previous coronary artery disease, and were treated with EPCLUSA during HCV infection. 

WARNINGS AND PRECAUTIONS Risk of HCC Reactivation In Patients Cofected with HCV and HBV HBV reactivation has been reported in HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals in patients with HCC. These patients have been reported in HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals. Of the 3 patients in whom HCC was diagnosed, 2 patients had an underlying HBV infection, and 1 patient had cirrhosis. 

ADVERSE REACTIONS Most common adverse reactions (greater than or equal to 10%, all grades) for EPCLUSA with ribavirin were headaches and fatigue; EPCLUSA and ribavirin were discontinued in 15% and 12% of subjects, respectively. Subjects with genotypes 4, 5, or 6 HCV, who received EPCLUSA for 12 weeks. Aspartate aminotransferase concentrations increased in patients with anemia (8%), nausea, headache, insomnia, and diarrhea. Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in a Phase 3 trial (ASTRAL-1) showed a relationship to drug exposure. 

STUDY DESIGN AND POPULATION Patients with genotypes 1, 2, 3, 4, and 6 HCV infection, who received EPCLUSA for 12 weeks. 

Common adverse reactions (at least 10%) were headache and fatigue; EPCLUSA and ribavirin were discontinued in 15% and 12% of subjects, respectively. Subjects with genotypes 4, 5, or 6 HCV, who received EPCLUSA for 12 weeks. Aspartate aminotransferase concentrations increased in patients with anemia (8%), nausea, headache, insomnia, and diarrhea. Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in a Phase 3 trial (ASTRAL-1) showed a relationship to drug exposure. 

Acute Kidney Injury: The use of ribavirin requires close monitoring for HCV treatment. In patients with genotypes 1, 2, 3, 4, and 6 HCV, who received EPCLUSA for 12 weeks. Aspartate aminotransferase concentrations increased in patients with anemia (8%), nausea, headache, insomnia, and diarrhea. Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in a Phase 3 trial (ASTRAL-1) showed a relationship to drug exposure. 

Drug Interactions Sofosbuvir and velpatasvir are substrates of P-gp and breast cancer resistance protein (BCRP) and inhibitors of OATP2B1. Coadministration of EPCLUSA with drugs that are substrates of P-gp and/or BCRP, leading to potentially reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended. EPCLUSA may be used in patients with genotype 1 HCV who are on dialysis and/or using a drug that is a substrate of P-gp and/or BCRP. These patients may increase the exposure of such drugs. 

Established and Potentially Significant Drug Interactions: The drug interaction profile is more complex in patients with cirrhosis because the components of EPCLUSA (sofosbuvir and velpatasvir) are individual agents, or agents with significant drug interactions. This list includes potentially significant interactions but is not all inclusive. Alteration in Dose or Regimen May Be Recommended For The 

Regimens containing tenofovir disoproxil fumarate (DF) are recommended for treatment of HCV infection. The addition of an antiviral/optimal combination of ribavirin. 

Renal Impairment: No dosage adjustment of EPCLUSA is required for patients with renal impairment or end stage renal disease (ESRD). EPCLUSA have not been established in patients with severe renal impairment (CrCl ≤30 mL/min) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD. Refer to the PB regimen prescribing information for guidance regarding dose adjustment in patients receiving hemodialysis. 

Hepatic Impairment: No dosage adjustment of EPCLUSA is required for patients with Child-Pugh class A, B, or C. 

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