What is the better move for 3 cm rectal polyp removal?

Articles by Norio Fukami, MD, and Gregory G. Ginsberg, MD. See page 4.
Note From The Editor

The first issue of 2016 features a debate on the best approach to removing large 3 cm polyps in the rectum: endoscopic mucosal resection vs. endoscopic submucosal dissection. The feature offers contrasting viewpoints from Drs. Gregory Ginzburg and Norio Fukami.

Also in this issue, from the perspective of hepatology, Dr. Joseph Ahn examines extraintestinal manifestations of HCV, while Drs. Nicole Loo and Michael Leise provide updates on the approach to treating noncirrhotic portal hypertension.

Other topics covered in this issue include screening for Barrett’s esophagus, optimal endpoints for IBD therapy, timing of interventions for complications of acute pancreatitis, and how best to handle residual symptoms after treatment of celiac disease. Additionally, the electronic medical record is here to stay and Dr. Peter Kaufman provides some practical information for practitioners on how to best handle cybersecurity in the Information Age.

I am excited to let you know that the new year also brings a new website for AGA Perspectives, which you can visit at www.agaperspectives.gastro.org. The new site provides a unique online home for AGA Perspectives, allowing readers to view current and past issues at any time, from any device. I hope you will find our new online presence innovative and informative.

Best,

Gary W. Falk, MD, MS, AGAF
WHAT’S THE BETTER MOVE FOR 3 CM RECTAL POLYP REMOVAL?
Endoscopic mucosal resection (EMR) uses adjunctive techniques to achieve curative resection of neoplastic lesions limited to the mucosal layers that are not amenable to cure using standard snare resection techniques alone. A flat, 3-centimeter, rectal lesion is well suited for EMR by initial injection of a submucosal fluid cushion, followed by confluent, wide-area, piecemeal snare resection. This saline-assisted EMR technique is safe, effective, fast, uses off-the-shelf routine accessories and has been part of the GI endoscopist’s armamentarium for close to 20 years, winning broad adoption. By contrast, endoscopic submucosal dissection (ESD) is a technique that was initially developed and refined in Asia for the en bloc resection of early mucosal gastric cancer. Although ESD has been demonstrated to be an effective technique for resection of large mucosal lesions, it has not been widely adopted in Western countries for the following reasons: lower incidence of early gastric malignancies, increased technical challenge of the procedure, lack of training and expertise, longer procedure duration, inadequate reimbursement and higher risk of complications. Even in Japan, colorectal ESD is performed only by a small, dedicated group of practitioners.

Wide-area EMR is extremely safe for laterally spreading rectal adenomas. Perforation and transmural bowel syndrome are rare and are related to the location distal to the retroperitoneal reflection. Acute bleeding is uncommon. When it occurs, it is readily treated with routine hemostatic techniques and should not interfere with completion resection. We previously reported a delayed bleeding rate as high as 7 percent following resection of colonic neoplasms greater than or equal to 2 centimeters in diameter.6 However, virtually all the delayed bleeding cases occurred with right colon lesions. Clinically significant bleeding with ESD for a rectal lesion occurs at comparable rates. Massive air extravasation of insufflation gas with pneumoretroperitoneum, pneumomediastinum and subcutaneous emphysema has been described during rectal ESD, and so the procedure should only be undertaken with the use of CO2 gas to mitigate this potential complication.3 In expert hands, both EMR and ESD have comparable safety levels for the curative resection of a flat, 3-centimeter rectal lesion.

Both EMR and ESD also achieve effective contour reproduction of laterally spreading rectal adenomas limited to the mucosa, including those with intramuscular carcinoma (T1a). However, lesions with early invasive carcinoma into the submucosal layer (T1b) pose challenges to management. Depth of submucosal invasion is associated with an incrementally increased risk for concurrent lymph node metastases in the context of the other histopathological prognosticators of depth of invasion, tumor grade and presence of lymphovascular invasion. Fortunately, these make up only a very small percentage of flat, 3-centimeter rectal lesions. En bloc EMR is generally relegated to lesions less than or equal to 2 centimeters. Piecemeal resection is typically required for a 3-centimeter lesion. ESD offers the potential to provide an intact resection specimen with minimal thermal injury, and thus preserves the architecture for staging. However, published series of ESD for rectal lesions report intact margins in as low as 67 percent of cases.1

There is a higher rate of local residual/recurrent adenoma observed at follow-up surveillance endoscopy compared with resecting EMR versus ESD. However, surveillance endoscopy is necessary after both procedures, the focal residual/recurrence is readily recognized and is readily eradicated with additional resection/ablation. In our large colorectal neoplasms of ESD over EMR for the vast majority of the reason, decreasing in procedure cost and duration.

The potential value of ESD over EMR for colorectal neoplasms cannot be reconciled with the marked increases in procedure cost and duration.

Creating large flat polyps in the rectum can be quite challenging for endoscopists. Among other things, the difficult location of rectal polyps — such as ones in the lower rectum or near the rectosigmoid junction — may affect endoscopic accessibility and stability, and limit snare maneuverability. One method of treatment, endoscopic mucosal resection (EMR) of polyps, is especially difficult in the low rectum where the correct approach for endoscopes and snare is not always straightforward or clear. Technical challenges limit the size of each tissue resection with both conventional and advanced snare of variable sizes. Thus, piecemeal resection is often the answer to the endoscopic treatment of large rectal polyps. We have learned to live with this imperfection. Piecemeal resection is currently the preferred method for larger polyps, with the goal of complete eradication, or at the very least, a reduced risk of perforation. We had no other methods than to cut large polyps into pieces and we accepted the risk for residual polyp or neoplasm. This resulted in an unclear or positive margin for cancer if a proper resection plan was not carefully sought, requiring patients to undergo additional surgery or to live with uncertainty regarding a cure. We know that surgeons would not try to cut any tumor into pieces.

Another method, endoscopic submucosal dissection (ESD), was developed for endoscopists as a new endoscopic resection technique that allows for the large “en bloc” resection (removal in one piece) of polyps that are even larger than 3 centimeters in size. This method, which shares many similarities to the surgical techniques, allows us to think more like oncologic surgeons, and it is time for this paradigm shift.

First, we need to discuss and evaluate the configuration of the polyp prior to the resection. A flat polyp of 3 centimeters in diameter is classified as a laterally spreading type (LST) lesion.1 There are two types of LSTs, one is a granular type and the other is a non-granular type. Granular type lesions are less likely to harbor invasive cancer compared with non-granular type lesions, and it is usually easier to perform conventional endoscopic mucosal resection on granular type polyps, although usually in a piecemeal fashion.1,2 Previous attempts at removal were shown to be a significant independent risk factor for EMR failure and recurrence, and therefore it is important to employ the most appropriate and successful technique during the first attempt at removal. Risk for the presence of invasive cancer increases with “Paris classification 0-Ia-Ib, non-granular type, and loss of pit pattern (Kudo’s pit pattern V) and “loss of pit pattern (Kudo’s pit pattern V)” large nodules>1cm, depressed area, sclerotic wall, redness and tumor size >20mm2. Cancerous portions should be identified and removed within a negative margin (both deep and lateral margins) to ensure that a proper assessment for oncologic curative resection can be completed following removal.

We also need to develop strategic resectioning plans for both piecemeal and en bloc polyp removal. These polyp segments that have been endoscopically identified as having the most advanced pathology, e.g. large nodules or depressed areas, should be removed first if en bloc resection is likely to be unsuccessful and piecemeal resection be performed. Then, the remaining portion of polyp can be removed subsequently. It is often difficult to remove flat or depressed polyps via EMR or through conventional fluid cushion assisted polypectomy due to the difficulty of capturing adequate neoplastic tissue into the snare, which results in multiple, small resection pieces. Thus ESD is a better option for these types of polyps. Recurrence after piecemeal resection was ENDOSCOPY SUBMUCOSAL DISSECTION IS A BETTER OPTION FOR PHYSICIANS AND PATIENTS WHEN IT COMES TO LARGE RECTAL LATERALLY SPREADING TUMORS, ESPECIALLY WHEN POLYPS SHOW SIGNS OF ADVANCED PATHOLOGY.

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EMR was recommended to undergo surgery in the Australian study. However, 71 to 77 percent of T1 cancers had only shallow invasion into the submucosal layer (<1000μm) in the Japanese studies, which falls into the low risk criteria for lymph node metastasis and may allow these patients to avoid surgery.

Appropriate planning for the resection and technique, including imaging material and method, starting location, snare size and stiffness, and a sequence of resection, is of the upmost importance for optimal outcomes with EMR. Alternatively, ESD principally aims for en bloc resection of lesions with negative margins, thus always aiming for oncologic resection. In addition, en bloc resection is ideal for detailed pathological assessment for oncologic resection.

Endoscopic resection for rectal lesions is a more beneficial option than surgery, as the location is safest for ESD and is shown to be less technically challenging for endoscopists. Thus, endoscopic submucosal dissection is a better option for physicians and patients when it comes to large rectal laterally spreading tumors, especially when polyps show signs of advanced pathology.

EMR references:

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2. Buchner AM, Guarner-Argente C, Ginsberg GG. Anymore. ESDD - CONTINUED FROM PAGE 7
e are all aware that the incidence of esophageal adenocarcinoma has been rising rapidly over the last 50 years. Since the cancer is associated with an endoscopically visible lesion in Barrett’s esophagus, screening for esophageal adenocarcinoma ought to be relatively easy compared to screening for other terrible cancers, such as pancreatic or ovarian. But there are many reasons why screening for esophageal adenocarcinoma may not be as effective as one would hope. For instance, surveillance biopsies may be insufficiently obtained in time or space; patients at greatest risk for the cancer typically are at greatest risk of competing causes of death, such as cardiovascular disease, and patients who are least likely to respond to endoscopic therapy appear to have the highest baseline risk of progressing to cancer to begin with. For the sake of argument, let’s assume that screening for esophageal adenocarcinoma is indeed worthwhile despite those shortcomings. In that case, who should we screen?

Consider first how well we are doing currently in screening. Nationally, we perform roughly 2 million upper endoscopies a year in patients with symptoms of gastroesophageal reflux disease (GERD), costing society over $1 billion annually. And despite all of those endoscopies, fewer than 15 percent of patients with esophageal adenocarcinoma have undergone an upper endoscopy prior to their presentation with the cancer. It is quite clear that we are performing a colossal number of scopes, but in the wrong patients.

A major problem with our current approach is that a slight majority of patients with esophageal adenocarcinoma actually deny having had prior GERD symptoms of note.1 And the patients that we do scope with GERD symptoms are usually the patients whose symptoms have not responded adequately to proton pump inhibitors. Often these patients have atypical symptoms such as throat clearing or globus sensation, often with substantial comorbid anxiety, and they are unlikely to actually have pathological reflux as a cause of their symptoms. The patients who present with esophageal adenocarcinoma, if they have GERD symptoms at all, often tell me that they have had heartburn for years but just took over-the-counter antacids and never discussed their symptoms with a doctor since they were managing fine. If screening is to effectively reduce the burden of esophageal adenocarcinoma, it will need to rely on primary care providers or even the public health service to identify appropriate patients for screening. Relying on gastroenterologists to screen patients among the highly selected population of patients referred for consultation for refractory symptoms is a failed strategy.

So which individuals are the ones who should be screened? The highest risk patients are white men over the age of 50 or 60 who have experienced years of heartburn or regurgitation, have used tobacco and have abdominal obesity.2, 3 But if we only screened that group of patients, we would have a limited impact on the burden of the cancer. Additional groups of patients could include men above 50 or 60 years of age with either GERD symptoms or a combination of abdominal obesity and tobacco use. Family history of esophageal adenocarcinoma in a first-degree relative might also be a reasonable indication for screening, irrespective of whether the patient has GERD symptoms. On the other hand, women of any age are at very low risk for esophageal adenocarcinoma, even if they have GERD symptoms.

None of the known risk factors for Barrett’s esophagus or esophageal adenocarcinoma have extremely high odds ratios. And the incidence of esophageal adenocarcinoma in the general population is still quite small (2.5 per 100,000 patients per year). So we can’t really identify patients who are at high risk. The best we can do with currently known risk factors is to identify the patients who are not at exceedingly low risk like the rest of the general population. It may not be a wise use of our society’s resources to screen for Barrett’s esophagus under such circumstances when the screening tool involves a highly trained (and expensive) endoscopist with a staff of nurses, technicians, monitoring equipment and possibly an anesthesiologist. Alternative methods exist. Transnasal unsedated endoscopy removes much of the cost associated with sedated endoscopy, and non-endoscopic devices also hold promise. One such device, the cytosponge, is an abrasive sponge contained within a pill-sized capsule on a string that a nurse or technician can administer. After swallowing the capsule with water, the gelatin capsule dissolves and the sponge is pulled out, obtaining a semi-histologic quality cytology specimen that appears to be quite accurate for identifying Barrett’s esophagus. It may even be validated for identifying dysplasia. If such devices are very low cost (meaning something like $100 including analysis), then screening a wide enough spectrum of the population to capture most patients who are destined to develop the cancer might finally be an efficient strategy of screening for esophageal adenocarcinoma.

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REFERENCES

In 2015, the ultimate nonhepatic manifestation of HCV may indeed be the headaches and frustrations that arise from the challenges facing providers, staff and patients. In 2016, the ultimate nonhepatic manifestation of HCV may indeed be the headaches and frustrations that arise from the challenges facing providers, staff and patients. As I ponder these headaches, I sometimes wonder how my patient is doing. She decided to move closer to her grandchildren after taking an early retirement. I hope she's cured of her HCV and healed of her mixed cryoglobulinemia, because, at that time, all I could do was refer her medications and give her a prescription for hope, with the promise that things would get better in the future. I just pray that this prescription will soon be filled for all patients with HCV.

Nonhepatic manifestations, which are also referred to as extrahepatic manifestations of HCV, have been widely reported in the literature. However, their frequency in HCV patients and verification of a direct pathophysiologic association with HCV has been less clear. Mixed cryoglobulinemia is a classic nonhepatic manifestation of HCV and is the paradigm for the wide spectrum of disease in nonhepatic manifestations varying from mild palpable purpura to glomerulonephritis or life-threatening vasculitis. Non-Hodgkin’s lymphoma remains another diagnosis strongly associated with chronic HCV. My patient presumably had mixed cryoglobulinemia, which manifested on days when she worked longer hours as a florist or when she flew out of state to visit her grandchildren. But she also had diabetes, nonspecific muscle pain and a growing fatigue that belied her cheerful disposition. This all made it difficult for her to finish shifts on her feet, and at that time, I could offer little beyond encouragement. However, there is now increasing awareness of the risk of insulin resistance, cardiovascular disease, severe fatigue or cardiovascular disease, were considered to be poor candidates for IFN. Even if patients started on IFN, the rates of sustained virological response (SVR) were suboptimal, and some of those patients who were lucky enough to reach SVR found they still retained symptoms.

With the advent of directly acting antivirals (DAA), which have been shown to have significantly higher rates of SVR, easier tolerability and improvements in quality of life, the growing recognition of HCV as a systemic disease that diminishes the patient’s overall health and quality of life poses new challenges to providers and payers in prioritizing the care of these patients. Those patients previously labeled as poor candidates for IFN may have ironically been those with the greatest need for treatment, even independent of their hepatic disease status. A practical acknowledgment already appears to have occurred as many payors consider nonhepatic manifestations of HCV in prioritizing the care of these patients. Further studies are needed on the pathophysiology of these manifestations and optimal management strategies, including the possibility of treatment to improve quality of life and even perhaps, to prevent development of nonhepatic manifestations.

In 2016, the ultimate nonhepatic manifestation of HCV may indeed be the headaches and frustrations that arise from the challenges facing providers, staff and patients as they struggle with the reality that given the costs of DAA treatment, the diagnosis of HCV does not equal access to treatment. As I ponder these headaches, I sometimes wonder how my patient is doing. She decided to move closer to her grandchildren after taking an early retirement. I hope she's cured of her HCV and healed of her mixed cryoglobulinemia, because, at that time, all I could do was refer her medications and give her a prescription for hope, with the promise that things would get better in the future. I just pray that this prescription will soon be filled for all patients with HCV.

The problem recently, in the age of interferon, has been that nonhepatic manifestations of HCV have been underdiagnosed, and understudied due to limitations in the understanding of its pathogenesis, along with practical challenges posed by the toxicity of available therapies. Treatment options were further constrained because IFN was acknowledged as a possible risk for life-threatening exacerbation of nonhepatic manifestations. In addition, patients with the above-mentioned possible nonhepatic manifestations of HCV, such as psychiatric disease, severe fatigue or cardiovascular disease, were considered to be poor candidates for IFN. Even if patients started on IFN, the rates of sustained virological response (SVR) were suboptimal, and some of those patients who were lucky enough to reach SVR found they still retained symptoms.

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n the realm of inflammatory bowel disease (IBD), endpoints can be based on many things. We commonly use subjective assessments and complement these with more objective evaluations, including laboratory, endoscopic and radiologic studies. A great deal depends on the context in which these are considered: are they in reference to a clinical trial or to assess response in an individual patient or to assess response in a clinical trial of a new biologic agent? Research studies and drug development demand scores allowing for consistent patient selection, quantification of the proportion of patients responding based on the rules of the study, and allowing comparisons across patients and between studies. By contrast, metrics for the individual patient can be and should be far more nuanced. A patient-specific response should take into account the patient’s overall well-being, most bothersome symptom, individualized treatment goals and objective assessments of inflammation. Historically, subjective scales have dominated assessments in clinical trials. These include the Crohn’s disease activity index for Crohn’s disease and the Mayo score for ulcerative colitis. However, it is worth noting that both have subjective parameters. The Crohn’s disease activity index includes weight and anemia, and the Mayo score includes endoscopy. Finally, the IBD Questionnaire is a validated instrument measuring quality of life. Most studies include it as a secondary endpoint and generate a graph of the data, but generally it is not used to gauge drug efficacy.

Recently, IBD treatment endpoints have come under scrutiny because of two competing issues in the field. The first is FDA and patient-led efforts to focus on patient-reported outcomes, which has led to a distillation of all IBD endpoints into primarily two things: number of bowel movements and abdominal pain. Given that these outcomes were derived from trials, they are not truly independent of the “old” scales. Now that we are left with only two things to assess, we all miss the Crohn’s disease activity index.

On the other extreme, inflammasome ushered in the era of mucosal healing. So what about mucosal healing as an endpoint? In particular, what does mucosal healing mean in trials versus practice? Several instruments have been validated for assessment of endoscopy in IBD. In Crohn’s disease, the Crohn’s disease Endoscopic Index of Severity is the most detailed and has a shortened sister version, the Simple Endoscopic Score. The abridged version does not capture the depth of the ulcerations, which we know to be important for prognostication. There is also the Rutgeert’s score, which measures neoterminal ileal disease recurrence after ileocolic resection. The Mayo endoscopic score looks at the severity of the inflammation in ulcerative colitis. It has been criticized because of inter-observer variability and improved upon by recent studies that tested and validated the ulcerative colitis endoscopic index of severity.

Now comes the devil in the details: how much mucosal healing does one need in order to say that a patient is mucosally “healed”? In recent clinical trials of biologics for IBD, it is surprising to see how the definition varies — some allow persistence of mild inflammation and some require no inflammation. As clinicians and investigators, we would like to see all studies providing data reflecting complete mucosal healing and those with a substantial improvement compared to their baseline. One can understand that a patient with very limited mucosal inflammation is more likely to have complete healing with a therapy whereas one with deep ulcerating disease may have substantial improvement in their ulcerations that is actually more meaningful and more difficult to achieve.

In addition to endoscopy, there are other important ways to assess disease activity and therapeutic endpoints less invasively. C-reactive protein (CRP) is a reasonably specific marker of inflammation in patients with IBD without other co-morbidities, though flawed by the fact not all individuals generate CRP (because of genetic polymorphisms) and because small bowel disease is less likely to induce c-reactive protein. Likewise, fecal calprotectin has emerged as a sensitive and specific marker in IBD, but again is of limited use in those with small bowel disease. Each provides complementary data. It is best to think of these tests like an ammonia level, important to know a baseline and follow the course as encephalopathy improves. Finally, radiologic tests are not only useful but, for a given patient, may be the only way to follow small bowel disease activity or look at perianal fistula tracts. For magnetic resonance enterography, the MABA score (not named for the author) tracks well with severity of disease and response to therapy.

In terms of individual endpoints, several things must be considered concomitantly including patient symptoms, disease severity, and risk of progression or complications of disease. Clinicians seeing an IBD patient should have a standard way to query patients and identify those that are most bothersome for that patient. A simple “how do you feel?” is insufficient. Although number of bowel movements and abdominal pain are reasonable places to start, some patients are filled by fatigue, by urgency and fear of incontinence, and others by pain. Therefore, establishing what they most want to accomplish with therapy is essential. This becomes especially important for a seemingly asymptomatic patient, who has either become accustomed to a lower quality of life and does not remember “normal” or is truly asymptomatic and the clinician must therefore have a clear reason to treat the patient (e.g., deep ulceration, shortened small intestine) since medications cannot make them feel any better. In Atul Gawande’s new book, “Being Mortal,” he highlights a physician’s task of establishing a patient’s therapeutic goals and how much they are willing to risk to achieve them. One would be surprised by what patients really want.

The ultimate endpoint of therapy would be a cure. Unfortunately, we are not there yet. But many have witnessed firsthand the transformation possible with current therapies. About 20 percent of patients on biologics experience complete mucosal healing.1 Not surprisingly, ample studies demonstrate these lucky patients who do achieve mucosal healing do better, with fewer hospitalizations and surgeries. Based on these data, the aspirational goal should be complete mucosal healing. Indeed, histologic remission, especially in ulcerative colitis, is emerging as even more important than mucosal healing alone. In a recent study, we found patients may have adequate serum levels of anti-tumor necrosis factor (TNF) agents and yet the intensity of the inflammation and local TNF production may outstrip the available anti-TNF in the tissue.2 Thus, operationally it is not always possible to give sufficient anti-TNF to achieve mucosal healing.

The authors suggest establishing individual treatment endpoints prior to starting new medications. First, have a clear understanding of the patient’s most bothersome symptom and the degree and extent of inflammatory disease using the tools described above (see figure on the next page). The choice of therapy is beyond what can be described here but should be appropriate for the degree of inflammation and patient-specific

References:
APPROACH TO ASSESSING AN IBD PATIENT

SYMPTOMS

• Mild (bothered but functions at a normal capacity)
• Moderate (affects daily life)
• Severe (close to or needing hospitalization)

SEVERITY OF INFLAMMATION

• Superficial ulcerations
• Deep ulcerations/inflammatory structure
• Fibrotic structure
• Internal perforating disease (+/- abscesses)
• Penetral perforating

REFERENCES

1. Travis SP et al. Mucosal healing and patient-specific risk factors, pushing to current therapy. Depending on these goals and patient-specific risk factors, pushing to mucosal healing may be ideal but has to be tempered by the risk of doing so. Along the way, keep in mind adjunctive agents like anti-diarrheals that may have dramatic benefits on the endpoints for the patient. In the sum, the endpoints of IBD therapy should be a balance focusing on patient goals and also patient-specific characteristics.


LOCATION

• Limited ileal disease
• Extensive small bowel involvement
• Extensive colonic involvement
• Rectal disease

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HARVONI IS NOT RECOMMENDED FOR USE WITH OTHER PRODUCTS CONTAINING:

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 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.

- 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.

- Coadministration of HARVONI is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

- Coadministration of HARVONI is not recommended with simprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with ritonavir-boosted protease inhibitors (PIs), including ritonavir-boosted indinavir, ritonavir-boosted lopinavir, ritonavir-boosted atazanavir, and ritonavir-boosted saquinavir.

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RISKS OF SERIOUS SYMPTOMATIC BRADYCARDIA WHEN COADMINISTERED WITH AMIODARONE:

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- Coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tienaprevir/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 simprevir 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.
Studies in rats have demonstrated that fatigue and headache. Related by the investigator: The most common adverse reactions (≥10%; all grades) were related to the 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 (10%); diarrhea (9%); 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.

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 (10%); diarrhea (9%); and insomnia (5%)
- HARVONI for 24 weeks: fatigue (18%); headache (17%); nausea (9%); diarrhea (7%); and insomnia (6%)

Brief Summary (cont.)
- Proton-pump inhibitors: Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasting conditions.
- Antihypertensives (amlodipine; digoxin) Amlodipine: Co-administration of HARVONI with amlodipine at a dose of 5 mg, a once-daily dose, may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, calcium blockers other than diltiazem or verapamil should be used. Digoxin: Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.
- Anticonvulsants (carbamazepine; phenytoin; phenobarbital; phenobarbital) Dosages of greater than 1.5x higher than predicted ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- HIV Antiretrovirals

- Regimens containing tenofovir disoproxil fumarate (TDF) and an H2 protease inhibitor/NNRTI/INT (tenofovir DF plus zidovudine/lamivudine, darunavir/ritonavir or lopinavir/ritonavir) The safety of increased tenofovir concentrations has not been established. Consider alternative HIV or antiretroviral therapy, if coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIEVAIR, TRUVADA, or ATRIPLA prescribing information for renal monitoring recommendations.
- Elvitegravir/tenofovir alafenamide DF: Monitor for tenofovir-associated adverse reactions. Refer to VIEVAIR, TRUVADA, or ATRIPLA prescribing information for renal monitoring recommendations.
- Entecavir/tenofovir alafenamide DF: Safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.
- Tenofovir/rilpivirine: Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- HCV Products (sofosbuvir): Increased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.
- Oral Antiviral Inhibitors: Changes in ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- Orally Active P-gp Modulators: Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- HIV Protease Inhibitors
- Inducers: P-gp inducers, such as rifampin, rifabutin, iraconazole, and nelfinavir. Coadministration is not recommended.

- Metabolism

- Reduced ledipasvir and sofosbuvir concentrations may lead to a reduced HARVONI effect. Use of HARVONI with P-g inhibitors (e.g., rifampin or St. John's wort) is not recommended.

- Reduced Product Not Recommended: Use of HARVONI with products containing sofosbuvir (SOVALDI) is not recommended.

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- HARVONI for 12 weeks: fatigue (13%); headache (14%); nausea (10%); diarrhea (9%); 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 levels of greater than 3x ULN were observed in ≤1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. Lactate Elevations: Transient, asymptomatic increase in lactate 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. 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.

Risk of Reduced Therapeutic Effect Due to P-gp Induction: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-g inhibitors (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 Phase 3 clinical trials in subjects with genotype 1 CHC with compensated liver disease (with and without cirrhosis) who received HARVONI for 8 (N=212), 12 (N=539) and 24 (N=420) 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.
A subset of patients will progress to severe necrotizing pancreatitis. These are the patients who are most likely to benefit from the latest developments in treatment. First, it is important to recognize that the presence of necrosis alone is not an indication for intervention. However, what if we are faced with a patient who is early in his or her disease course and has persistent systemic inflammatory response syndrome or signs of organ failure in the setting of pancreatic necrosis? Infected pancreatic necrosis within the first week of disease onset is exceedingly rare. At this stage of illness, the emphasis would be appropriately placed on the provision of maximal supportive care that includes enteral nutritional support. In terms of timing, the evidence supports an ‘on-demand’ approach such that enteral nutrition is started once it becomes clear that a patient is unlikely to resume oral intake within the next few days, for example in the setting of protracted pain, acute respiratory failure or hemodynamic instability.

Another critical aspect in the management of necrotizing pancreatitis is the timing of intervention. During the first several weeks of acute pancreatitis, acute fluid collections are poorly organized and drainage procedures are unlikely to be effective at this stage. Therefore, delayed intervention is the current mainstay of treatment. How long should that delay be? Four weeks is often used as an estimate for appropriate timing for a drainage procedure. However, the primary consideration should be the adequate maturation of peri-pancreatic collection(s). A repeat cross-sectional imaging study performed prior to a planned intervention will provide critical information regarding the location and stability of a collection. Percutaneous, using a laparoscope, and endoscopic debridement have emerged as the two primary approaches to drainage of necrotic collections. At our institution, as in many other tertiary facilities, both approaches are available. We favor percutaneous debridement in patients with hemorrhagic instability who are unable to tolerate an endoscopic procedure. A key aspect of successful percutaneous debridement is the regular irrigation of the catheter. If necessary, upsizing the catheter can be helpful as well, and in select cases, can provide definitive management for these collections. Alternatively, endoscopic approaches can be very effective in managing collections located directly behind the stomach or duodenum.

Given the difficulty of determining the extent of necrotic material within a collection based on imaging alone, the endoscopist should be prepared to perform a direct endoscopic necrosectomy if necessary. Ultimately, a multi-disciplinary, team-based approach that leverages local expertise is needed to provide optimal care for these highly complicated cases of acute pancreatitis.

Finally, it is important to also note recent progress in the prevention of acute pancreatitis. In addition to prophylactic pancreatic duct placement, the use of rectal indomethacin is now widely accepted as an important measure for prevention of post-ERCP pancreatitis in high-risk patients. There is now level-one evidence supporting the efficacy of repeated alcohol cessation counseling in the case of alcohol-related acute pancreatitis and early cholecystectomy in the setting of biliary pancreatitis in the reduction of recurrent acute pancreatitis incidents.

In summary, there have been many exciting developments in the management and prevention of acute pancreatitis. Successful implementation of these approaches holds the promise of greatly improving outcomes for our patients.
As physicians, we should be concerned about this alarming trend. First, part of our job is to protect patients and work in their best interests. Second, none of us wants to lose trust. One survey found that 65 percent of consumers would avoid providers who had undergone a data breach. Third, HIPAA’s financial penalties are steep and government enforcement is on the rise.

The sad truth is that none of us is immune to these kinds of breaches. In the old days of paper records, stealing medical records usually meant someone local throwing a brick through the office window to gain access. Today’s threats are far more sophisticated, sophisticated, and wide-ranging: one is more likely to be targeted anonymously from thousands of miles away. The human factor and the unavoidable errors of judgment that can lead to breaches are also real and constant, which means staff must be screened and trained continuously. Because new threats are always emerging, one needs to practice constant vigilance and updating of systems and software. That’s something most practices don’t have the time, resources or expertise to do.

Unfortunately, there is no simple answer and no perfect fix. Attempts to improve cybersecurity will inevitably involve trade-offs in terms of time, money, effort and how much risk exposure your practice is comfortable with. As a practicing gastroenterologist and avid computer user who has some familiarity with EHR systems and basic computer security, I can offer the following general suggestions on what physicians can do to reduce the risks of cyberattacks and data breaches. (None of my suggestions should be interpreted as endorsements of any particular vendors or companies.)

- Talk to your EHR vendor. This is an excellent place to start. Some EHR vendors may be able to advise you on what your practice can do to routinely guard against security breaches. You may also want to ask your EHR vendor to explain what capabilities they use now and plan to use in the near future to help your practice guard against emerging threats.
- Don’t use default passwords or vulnerable passwords that can be easily guessed by hackers. Admin1234 is not a secure password. Yet, many practices still commonly use such passwords, according to the CEO of an EHR company with whom I recently talked (his company’s EHR system disallows use of such vulnerable passwords). Use longer passwords or passphrases (passwords with spaces; these can be short sentences that are easy to remember). Don’t use the same password for multiple programs. To avoid having personal email, Facebook, iTunes and photo downloading sites. That’s because accessing internet links leaves you susceptible to malware attacks and computer viruses. Either have separate computers for medical records, or use a virtual machine or a software application such as Citrix, which provides secure access to clinical applications, medical content and patient records. (I use one computer for both personal and work purposes, but always log in via Citrix for anything related to medical records.)
- Using secure access software like Citrix also allows users to securely access medical information from a remote or home-based computer. This is good if you or your staff need to get into medical records during non-business hours. If you are a small practice and can’t afford Citrix, you may want to look at remote desktop service applications that offer certificate-based or two-factor authentication. Again, ask your EHR vendor if they can help set that up or give advice.
- Conduct a cybersecurity audit or assessment once every year or two. This can identify vulnerabilities and risks in your system. Ask your EHR vendor if they can do this or recommend a company that can. Another option is to have your website scanned for potential vulnerabilities. There are several reputable companies that do this, including Tenable Network Security’s Nessus and Qualys, which offers a free online security scan.

Unfortunately, there is no simple answer and no perfect fix. Attempts to improve cybersecurity will inevitably involve trade-offs in terms of time, money, effort and how much risk exposure your practice is comfortable with.

- Remember lots of different passwords, consider using a password manager such as 1Password or LastPass.
- Vet and train staff. Staff need to know and be reminded not to give out their passwords or let their passwords be seen by others. They also need to avoid taking non-secured laptops out of the office period. Staff should also be advised not to leave in-office computers unattended without first logging off.
- Separate personal and business usage — or use two computers. Computers used to access medical records should not also run common internet-based applications, such as

**REFERENCES**


IBS and Persistent Symptoms in Celiac Disease

IBS is the most common intestinal disorder in our society, and is characterized by abdominal pain and altered bowel habit, in the absence of an underlying structural abnormality. IBS is often diagnosed by the costly exclusion of other diseases, which may include celiac disease — a chronic enteropathy triggered by gluten in persons with genetic predisposition. Despite an estimated worldwide prevalence of 1 percent, and the availability of specific diagnostic serological and pathological algorithms, celiac disease remains significantly underdiagnosed. When screening is actively undertaken by specific serology and biopsy, 4 percent of patients labeled as having IBS have underlying celiac disease, but this often goes undetected. Moreover, the burden and morbidity caused to those who suffer from the disease is underestimated. Since IBS is a symptomatic complex, in the absence of any discernible organic cause, a diagnosis of celiac disease should exclude IBS.

Once a clear diagnosis of celiac disease is established, the only current available treatment is a gluten-free diet for life, which is usually effective in improving symptoms and inducing mucosal recovery. However, the gluten-free diet is hardly an optimal therapy, and a substantial proportion of patients remain symptomatic despite efforts to adhere to the diet. This often relates to inadvertent or voluntary dietary transgressions in a substantial proportion of patients. One of the most common causes of persistent symptoms relates to continuous gluten exposure. Indeed, this has been reported in approximately 70 percent of celiac disease patients on a gluten-free diet.1 Until a pharmacological therapy that targets this patient population is approved and available, the best we can offer is education and treatment of the mucosal changes of celiac disease and true refractory cases, and professional dietary advice.

Although there are many possible causes for persistent symptoms in celiac patients who are on a gluten-free diet, an overlap with IBS has been proposed once other potential causes are ruled out. Such overlap should fall within the definition of IBS, and requires the exclusion of significant persistent mucosal inflammation or any other organic disease, food allergy or intolerance that could justify the symptoms. One of the proposed underlying pathways for symptom generation in IBS is low-grade inflammation, which could be induced by multiple stimuli including sensitivity to dietary components or infectious gastroenteritis. The same concept may apply to mucosal recovery after initiation of the gluten-free diet in celiac disease, and thus the residual low-grade inflammation might be associated with persistent symptomatology in some patients. This “post-celiac IBS” condition could eventually resolve or be perpetuated by other stimuli.

The question of whether there is true overlap between celiac disease in resolution and IBS onset cannot be clearly answered thus far. The question of whether there is true overlap between celiac disease in resolution and IBS onset cannot be clearly answered thus far, but it is reminiscent of the association between IBS in patients with inflammatory bowel disease.12 There is ample basic research evidence that inflammation impairs intestinal motor and sensory systems, altering gut function that can lead to symptom generation. Microscopic and functional rewiring of the neuromotor system of the upper gut after years of gluten exposure and inflammation in a celiac patient could explain some persistent symptomatology despite the gluten-free diet.

Finally, although basic research and emerging clinical reports suggest there could be a true overlap of IBS and celiac disease, the management of symptomatic celiac patients on a gluten-free diet should include more than a potential diagnosis of IBS. We must bear in mind that an IBS diagnosis is based on exclusion of organic causes, and therefore potential gluten exposure or contamination, true refractory cases and other overlapping diseases need to be ruled out first.

REFERENCES
cirrhosis is the most common cause of portal hypertension and varices in the Western world. However, varices can arise in patients with portal hypertension in the absence of cirrhosis or even in the absence of portal hypertension. This short perspective focuses on varices without cirrhosis, including background information and various diagnosis and treatment options.

Non-Cirrhotic Portal Hypertension

Portal hypertension, by convention, is subcategorized into pre-hepatic, hepatic and post-hepatic causes. This can be a very helpful framework to utilize when considering the myriad of causes of non-cirrhotic portal hypertension and varices, though it requires a basic understanding of venous pressure measurements. Direct measurement of portal vein pressure is invasive. Myers and Taylor (1953) first described the measurement of the wedge hepatic venous pressure, which was later validated by Grossmann and is now used to estimate the portal vein pressure. When the balloon occludes the hepatic vein (wedge pressure), it measures the hydrostatic pressure of the columns of blood beyond the balloon, which actually represents sinusoidal pressure. The sinusoidal pressure is an indirect measurement of portal vein pressure. The hepatic venous pressure gradient of 5 mm Hg or more is consistent with portal hypertension; however, values greater than 10 mm Hg are required for varices to be present (considered to be clinically significant portal hypertension).

The patient incidentally diagnosed with esophageal varices on upper endoscopy should undergo cross-sectional abdominal imaging with IV contrast. CT or MRI by itself is not sufficiently accurate for the diagnosis of cirrhosis. However, a constellation of findings should raise suspicion of underlying cirrhosis. In the absence of these findings, a reticulin stain can identify nodular regenerative hyperplasia characterized by micronodular transformation of the liver parenchyma, with central hyperplasia, an atrophic rim and no fibrosis. These varices are not treated with non-selective beta-blockers or with banding. The patient is therefore treated with selective beta-blockers.
such as a nodular shrunken liver, ascites, splenomegaly, intra-abdominal varices and a low pre-test probability of a treatable liver condition should dissuade the provider from a liver biopsy. In patients with a normal appearing liver on cross-sectional imaging, patent hepatic and portal veins, and abnormal liver tests, a liver biopsy should be pursued. While transient elastography has demonstrated lower stiffness levels (as expected) in idiopathic non-cirrhotic portal hypertension compared to cirrhosis, this modality is not sufficient for the diagnosis of idiopathic non-cirrhotic portal hypertension. A reticulin stain on liver histology should be requested to assess for nodular regenerative hyperplasia features, which are not obvious on H&E and trichome stains.

In patients with isolated gastric varices without evident cirrhosis, contrast enhanced CT or MRI should be performed to evaluate for splenic vein thrombosis. Spleenectomy is the treatment of choice in patients with splenic vein thrombosis and gastric varices. Varices in the upper third or the entire esophagus warrant further evaluation with a CT of the chest.

**Management of Non-Cirrhotic Portal Hypertension**

For patients with an identifiable cause of non-cirrhotic portal hypertension, such as primary biliary cirrhosis, disease-specific treatment should be initiated. The recently published Baveno VI Consensus Workshop summary reflects on the lack of data regarding prophylaxis for idiopathic non-cirrhotic portal hypertension and recommends following usual esophageal varices prophylaxis, which we agree with. Baveno VI guidelines recommend screening for portal vein thrombosis in idiopathic non-cirrhotic portal hypertension with Doppler ultrasound, though there is lack of evidence to support this practice. We generally do not include biannual Doppler ultrasound in our management of idiopathic non-cirrhotic portal hypertension.

**REFERENCES**


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