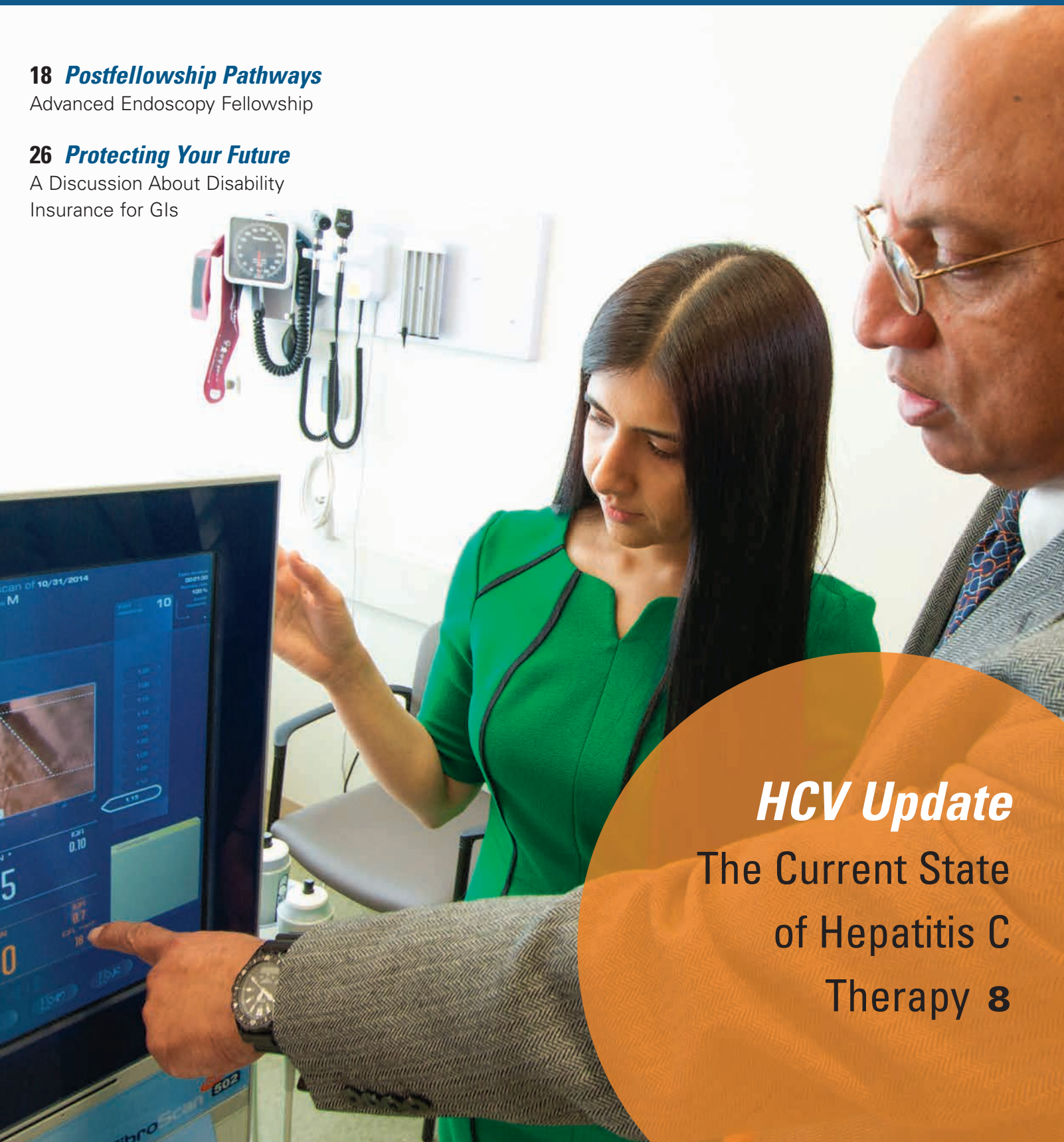
PREMIERE ISSUE

The NEW GASTROENTEROLOGIST

INSIGHTS FOR FELLOWS & YOUNG GIs

A Quarterly Supplement to GI & Hepatology News | Spring 2015



HCV Update

The Current State of Hepatitis C Therapy **8**

Letter
FROM THE EDITOR

Bryson W. Katona is a fourth-year gastroenterology fellow in the division of gastroenterology at the University of Pennsylvania, Philadelphia.

Dear Colleagues,

It is with great pleasure and excitement that I welcome you to the inaugural issue of the *The New Gastroenterologist: Insights for Fellows & Young GIs*, the AGA's newest publication dedicated specifically to the needs of fellows and young career gastroenterologists. As the Editor of *The New Gastroenterologist*, I am honored to have the opportunity to help develop and deliver this quarterly publication, which I, as well as the AGA leadership, hope will serve as a resource for not just young GIs, but also for the entire gastroenterology community. *The New Gastroenterologist* is the first publication of its kind within the field of gastroenterology and presents an exciting opportunity to concentrate content into a single place that specifically addresses the topics and issues that are common to all young career gastroenterologists. That being said, our goal for *The New Gastroenterologist* is to provide high-yield content that can be directly applied to your career and to deliver this content in a concise and easily readable format through a variety of features in each issue, including:

- Expert-authored updates on rapidly changing "hot" topics within the field.
- Perspectives on postfellowship career pathways.
- Articles on the "nuts and bolts" of pertinent financial and insurance topics.
- Inspiring personal stories from both our young and senior GI colleagues.
- Knowledge enhancement exercises including DDSEP©7 questions and clinical image challenges.
- Summaries and expert commentaries on recent high-impact articles from AGA's journals.
- And much, much more.

This issue of *The New Gastroenterologist* has a fantastic update on the current exciting state of HCV therapy as well as an inspiring story of a young GI's experience conducting research in Africa. Additionally, there is an insightful perspective about pursuing an advanced endoscopy fellowship, a primer on sample size and patient selection in small clinical studies, a discussion that focuses on the important aspects of disability insurance, and a variety of other interesting features. I truly hope that you enjoy this issue of *The New Gastroenterologist* and that you will look forward to future issues, which will be mailed quarterly with *GI & Hepatology News*, and will always be available freely online at www.gihepnews.com and www.gastro.org. We look forward to hearing your feedback, and we also welcome your ideas for future issue topics to ensure that *The New Gastroenterologist* successfully meets the needs of the young GI community. Please send questions or comments to me at bryson.katona@uphs.upenn.edu or Erin Dubnansky at edubnansky@gastro.org.

Sincerely,
Bryson W. Katona, M.D., Ph.D.
Editor

The NEW GASTROENTEROLOGIST

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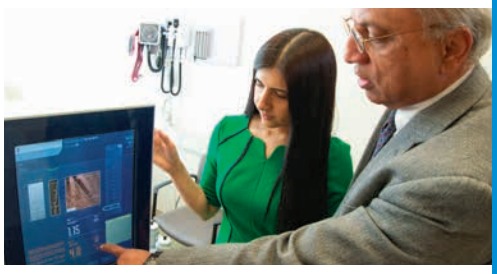
ON THE COVER

Dr. Vandana Khungar and Dr. K. Rajender Reddy of the University of Pennsylvania.

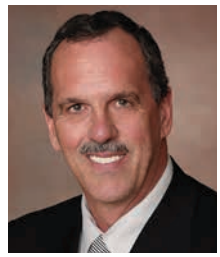
Photo by Nick Piegari, Frontline Medical News

IN THIS ISSUE



Welcome to the Inaugural Issue of

The NEW GASTROENTEROLOGIST



You're entering the gastroenterology field at an exciting time. Thanks to transformational policies and technologies, practice today is nothing like practice of yesterday – or tomorrow. And GI science is incredibly exciting and ripe for discovery.

As I was beginning my career in the early 1980s, we were changing from fiber-optic to video endoscopes, *Helicobacter pylori* was just recognized as the predominant cause of duodenal ulcers, hepatitis C was still called "non-A–non-B," and the molecular biology of colon cancer was a mystery. Imagine how far we have progressed since then. I envy the knowledge you will acquire during your career.

AGA keeps up with the trends and has an eye on what's next. Read *The New Gastroenterologist* to ensure you're knowledgeable and ready for the challenges ahead.

As you kick off your career, the AGA Governing Board welcomes you to the gastroenterology community. AGA is here to help you succeed.

Sincerely,
John I. Allen, M.D., MBA, AGAF
President, AGA Institute

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News from the AGA

Research Funding Opportunities from the AGA Research Foundation

The AGA Research Foundation has a variety of awards for junior investigators with deadlines in June 2015. Consider applying for the:

AGA-Athena Troxel Blackburn Research Scholar Award in Neuroenteric Disease
This new award will provide $90,000 per year for 3 years (total $270,000) to young investigators working toward independent careers in neuroenteric disease research.

AGA-Boston Scientific Career Development Technology and Innovation Award
This award provides $75,000 per year for 2 years (total $150,000) to young investigators working toward independent careers in gastroenterology, hepatology, or related areas focused on technology and innovation.

AGA Microbiome Junior Investigator Research Award
This award provides $30,000 per year for up to 2 years to junior investigators engaged in research related to the gut microbiome. Supported research may include basic, translational, clinical, or health services investigation.

To see complete application information, visit the AGA website (www.gastro.org) and click on "Research Funding." ■

ICYMI: Coverage from the AGA Clinical Congress

The 2015 AGA Clinical Congress took place in January in Miami. The news outlet *HCPLive* attended the meeting and has posted session updates and video interviews with the speakers. View their comprehensive meeting coverage (www.hcplive.com/conferences/aga-2015), which includes:

- A video interview with AGA President John I. Allen, M.D., MBA, AGAF, on navigating changes in medical practices.
- A video interview with AGA Practice Councillor Lawrence R. Kosinski, M.D., MBA, AGAF, on making value-based payments work in practice.
- Coverage of a session on the new age of treatments for hepatitis C. ■

AGA has 2 New Guidelines: HBV Reactivation and Pancreatic Cyst Management

Hepatitis B virus reactivation (HBVr) is a potentially serious disorder that can occur in the context of long-term use of immunosuppressive drug therapy. AGA's new guideline (published in the January issue of *Gastroenterology*) provides direction to GIs and patients who use immunosuppressive agents for the treatment of a variety of disorders, including gastrointestinal, dermatologic, neurologic, and rheumatologic, among others.

The recommendations included represent an evidence-based summary of literature describing the prevention of HBVr. Review of this guideline, in addition to the associated technical review, will facilitate effective shared decision making with patients at risk for HBVr.

Incidental discovery of asymptomatic pancreatic cysts is common with the increasing use of sophisticated abdominal imaging techniques. Clinical management is very difficult because only a small fraction of these lesions prove to be malignant, and the data to guide diagnostic and treatment decisions are sparse and of very low quality, based almost entirely on retrospective case series.

Nevertheless, AGA developed the guideline (published in the April issue of *Gastroenterology*) from the limited evidence that is available, because of the seriousness of the outcomes for that minority of cancers and the complexity of management strategies.

The two new guidelines were developed using GRADE (Grading of Recommendation Assessment, Development and Evaluation) methodology. To see all of AGA's guidelines and clinical decision support tools, visit the AGA website (www.gastro.org) and click on "Guidelines." ■

Trainee Track at DDW® 2015 Designed for Young GIs

AGA has developed special sessions at DDW® 2015 to meet the unique needs of physicians who are new to the field. Participants will learn about all aspects of starting a career in clinical practice or research, have the opportunity to network with mentors and peers, and review board material.

With the exception of the AGA Spring Postgraduate Course, all of the sessions are free, but you must register for DDW to attend.

AGA Spring Postgraduate Course: Evidence That Will Change Your Practice: New Advances for Common Clinical Problems – Saturday, May 16, and Sunday, May 17
Join your colleagues in Washington, D.C., to hear world-renowned experts present new medical evidence for six major areas of the GI tract. Discover need-to-know information and analyze data during a variety of interactive sessions. Trainees and young GIs may register at a reduced registration fee.

AGA Mentor and Advisor Program: Reception for Trainees/Young GIs: An Evening with AGA Mentors – Saturday, May 16
Meet your peers and more established colleagues who serve as mentors, while enjoying refreshments.

Board Review Session – Monday, May 18
This session, designed around content from DDSEP©7, serves as a primer for third-year fellows preparing for the board exam as well as a review course for others wanting to test their knowledge. Discount coupons for DDSEP©7 will be offered on a first-come, first-served basis.

Career and Professional Related Issues – Monday, May 18
Receive advice on career options in gastroenterology, learn what you need to know to find your first job from both a U.S. and international medical graduate perspective, and understand how the changes in health care will affect your future as a gastroenterologist.

Advancing Clinical Practice: GI Fellow-Directed Quality Improvement Projects – Monday, May 18
This trainee-focused session will showcase selected abstracts from GI fellows based on quality improvement, with a concluding state-of-the art lecture. Attendees will be provided with information that defines practical approaches to quality improvement from start to finish.

Visit the AGA website (www.gastro.org) and click on "Trainees" for additional details about Trainee Track sessions. ■

AGA Outlook

For more information about upcoming events and awards deadlines, please visit gastro.org.

Upcoming Events

MAY 8-9, 2015
Hepatitis B Management: State of the Art
Hudson Theater/Millennium Broadway
New York, NY

MAY 16-19, 2015
Digestive Disease Week
Walter E. Washington Convention Center
Washington, DC

MAY 16-19, 2015
Build Your Career at DDW 2015/Trainee and Young GI Track
Walter E. Washington Convention Center
Washington, DC

MAY 16-19, 2015
Diversity Special Interest Path: DDW Sessions for Minority Physician-Scientists
Walter E. Washington Convention Center
Washington, DC

AUG 29-30, 2015
2015 James W. Freston Conference: A Renaissance in the Understanding and Management of IBS
Chicago Marriott Downtown Magnificent Mile
Chicago, IL

NOV 10, 2015
ABIM Gastroenterology Certification Exam
May 15, 2015: Registration deadline
June 15, 2015: Late registration deadline

Awards Application Deadlines

AGA-Athena Troxel Blackburn Research Scholar Award in Neuroenteric Disease
Deadline: June 5, 2015

AGA-Boston Scientific Career Development Technology and Innovation Award
Deadline: June 5, 2015

AGA Microbiome Junior Investigator Research Award
Deadline: June 5, 2015

AGA R. Robert & Sally Funderburg Research Award in Gastric Cancer
Deadline: August 25, 2015

Research Scholar Awards
Deadline: October 16, 2015

What's Your Diagnosis?

A rare finding on evaluation for iron-deficiency anemia

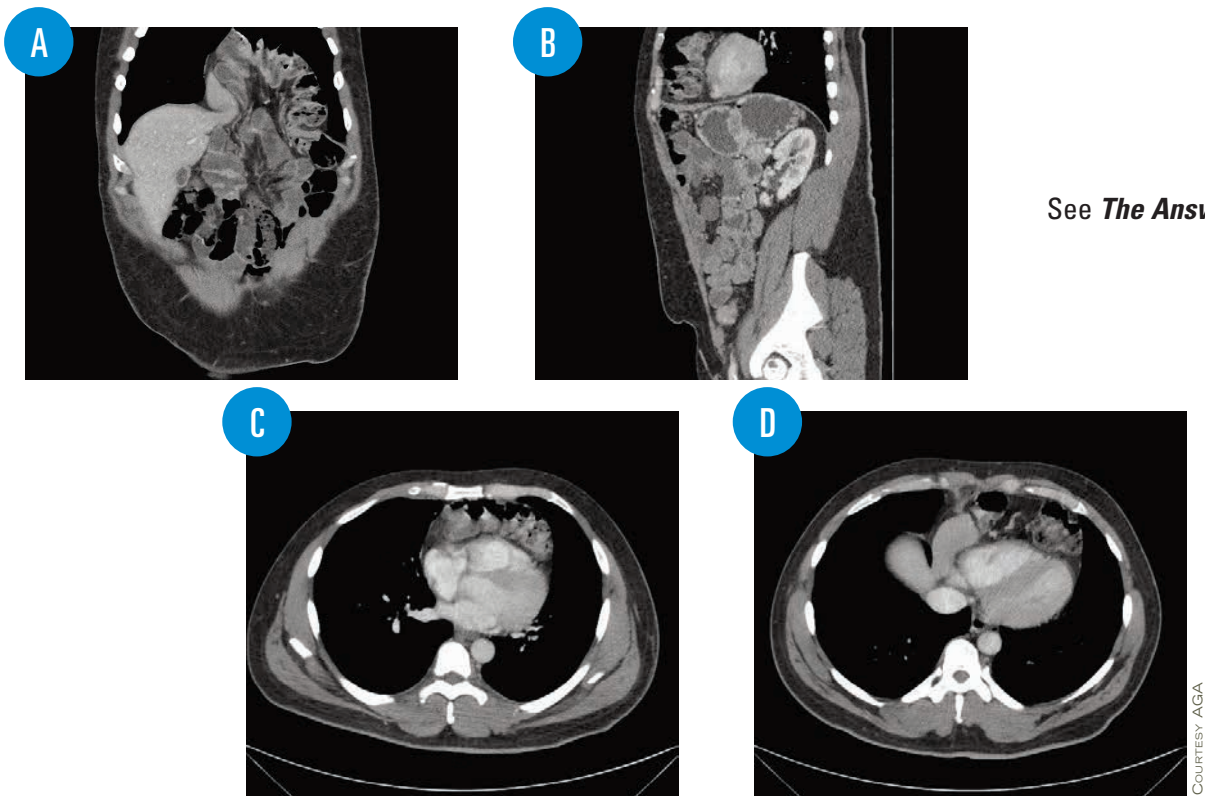
Published previously in Gastroenterology (2014;146:e8-9)

By Stephanie Judd, M.D., and Fadi Antaki, M.D.

A 53-year-old man with no significant past medical history was referred to gastroenterology for evaluation of iron-deficiency anemia. He denied melena, hematochezia, hematemesis, or any overt bleeding. He denied abdominal pain, dyspepsia, chest pain, or shortness of breath; complete review of systems was negative. General physical examination was within normal limits. Initial work-up included esophagogastroduodenoscopy, which was normal, and colonoscopy, which showed two adenomatous polyps. Video capsule endoscopy was subsequently completed, which showed possible extrinsic compression versus submucosal mass in the middle third of the small bowel. To further evaluate these video capsule endoscopy findings, computed tomography enterography was performed (Figures A–D). ■

What is the diagnosis, and how should it be managed?

Dr. Judd and Dr. Antaki are with the division of gastroenterology at the John D. Dingell VA Medical Center and Wayne State University in Detroit. Dr. Judd is also with the Detroit Medical Center.



Courtesy AGA

See ***The Answer*** on page 14

NICK PIEGARI/FRONTLINE MEDICAL NEWS

The Current State of Hepatitis C Therapy

By Vandana Khungar, M.D., M.Sc. and K. Rajender Reddy, M.D.

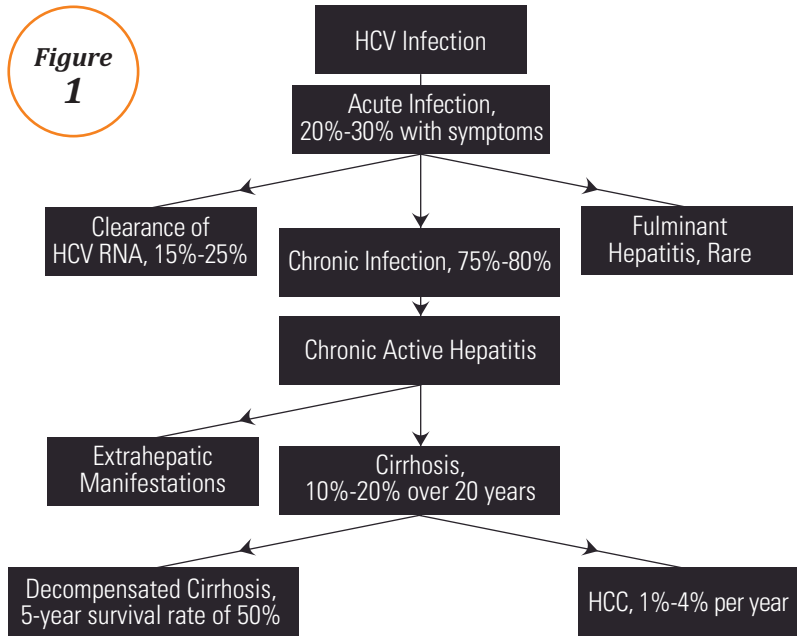
Dr. Khungar and Dr. Reddy are in the division of gastroenterology and hepatology, University of Pennsylvania, Philadelphia. Dr. Khungar reports no conflicts of interest; Dr. Reddy is on the advisory boards of Gilead, Abbvie, Merck, BMS, and Janssen.

Epidemiology, natural history, and historical perspective on the treatment of HCV

Hepatitis C virus (HCV) infection is a global public health issue that has received much attention because of the rising morbidity and mortality associated with HCV and also because of rapid advances in treatment options. Despite these advances, much is needed in the way of screening, treatment of chronic HCV, and care of patients with cirrhosis, end-stage liver disease, and hepatocellular carcinoma that are a result of this infection. HCV was first discovered in 1989 and is estimated to affect 170 million people worldwide and, by conservative estimates, 3 million Americans.[1] However, some believe that the true prevalence in the U.S. is closer to 5-7 million.[2] Most (80%-85%) of those acutely infected with HCV become chronically infected (Figure 1), with higher rates in those who are co-infected with HIV and with lower rates in women, children, and those with IL-28B CC genotype.[3,4] The feared complications of chronic HCV include cirrhosis, portal hypertension, hepatic decompensation, and development of hepatocellular carcinoma, all of which can necessitate liver transplantation in order to sustain life. HCV is estimated to cause 350,000 deaths annually.[5]

Therapeutic advances in the past few years have led us to realize the very real potential of an all-oral therapy regimen with greater tolerability and high rates of cure compared to earlier regimens. The goal of treatment of HCV is sustained virologic response (SVR), defined as absence of virus by the most sensitive virologic assay 12-24 weeks after cessation of therapy, and prevention of the progression of liver disease. There are six HCV genotypes with different structures requiring specific treatment approaches.

The standard of care until 2011 was pegylated interferon (PEG-IFN) plus ribavirin (RBV) and it was fraught with many side effects, as well as contraindications to treatment in those with severe psychiatric or autoimmune comorbidities. The first direct-acting antivirals, telaprevir and boceprevir (both NS3/4A protease inhibitors) were released in 2011 and were administered with PEG-IFN and RBV in triple-therapy regimens.[6] Boceprevir or telaprevir, compared with PEG-IFN/RBV alone, improved SVR rates and allowed for shortening of the duration of therapy in some patients to 24 weeks using response-guided treatment algorithms.[7] Such treatment, however, required very frequent HCV RNA testing, was associated with drug interactions, and led to new and more frequent adverse events (severe anemia requiring transfusion and dysgeusia for boceprevir; severe pruritus, rash, and anemia for telaprevir).[8] However, SVR rates were still poor in difficult-to-treat subgroups of genotype 1 patients (null responders with cirrhosis, interferon intolerant).[9,10] Within a short period of time, these therapies became obsolete and are currently no longer considered in the treatment of chronic HCV.



Courtesy Dr. Khungar and Dr. Reddy

Current management of HCV

Testing

Serologic tests for HCV include a screening assay for anti-HCV antibodies (HCV Ab), and a quantitative HCV RNA test. Indications for testing are noted in Table 1. In addition to these standard indications, if patients are at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV RNA is recommended as an anti-HCV antibody will be positive. If a patient's HCV Ab is negative and there is a high suspicion of active HCV infection, an HCV RNA test can be sent in this setting as well.

Treatment

Patients with active HCV infection should cease alcohol use and receive education and interventions aimed at reducing the progression of liver disease and preventing transmission of HCV. These patients should then be referred to a physician or nurse practioner/physician assistant well

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versed in HCV therapy, who can then provide comprehensive management and initiate treatment.

With newer direct-acting antivirals (DAAs), SVR rates are around 90% or higher across all genotypes, although the current treatment of hepatitis C remains genotype specific. The cost of preferred regimens ranges from approximately $63,000 to $150,000 in patients without cirrhosis and $84,000 to $300,000 in those with cirrhosis. The management of patients with renal impairment, HIV co-infection, acute hepatitis C, or post liver transplantation have challenges, are slightly more nuanced, and will not be the main focus of this article.

The HCV RNA genome carries all of the necessary genetic information to allow for effective HCV viral production, primarily within hepatocytes, and dissemination. The RNA genome is translated into a polyprotein that is then cleaved into individual proteins by proteases. All of the nonstructural HCV proteins – NS2-3 and NS3-4A proteases, NS3 helicase, NS5A, and NS5B – are essential for HCV replication, and are therefore potential drug discovery targets. The NS3/4A protease inhibitors (simeprevir, asunaprevir, paritaprevir, boceprevir, and telaprevir) are moderate to high potency with multigenotypic coverage and have an intermediate barrier to resistance. The NS5A inhibitors (ledipasvir, daclatasvir, and ombitasvir) have high potency with multigenotypic coverage and exhibit a low barrier to resistance. The NS5B nucleotide inhibitors (sofosbuvir) have intermediate to high potency with pangenotypic coverage and a high barrier to resistance, whereas the NS5B nonnucleotide inhibitors (dasabuvir) are in the low-potency category with limited genotypic coverage and have a low barrier to resistance (Table 2).

Treatment is currently recommended for patients with chronic HCV infection, including those with advanced fibrosis, compensated cirrhosis, liver transplant recipients (because of the rapid rate of fibrosis progression post transplant on immunosuppression), and patients with severe extrahepatic HCV. The introduction of DAAs into HCV treatment regimens increases the risk of drug interactions and close attention must be paid to the patient's medication list. This information is readily available through an interactive tool at www.hep-druginteractions.org. The most important drug interactions to remember are those of ledipasvir/sofosbuvir with acid-suppressing medications (lowering ledipasvir absorption) as well as the fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir with long-acting inhaled

Table 1 INDICATIONS FOR TESTING

One-time Testing	People born between 1945 and 1965 People who injected drugs in the past Recipients of clotting factor concentrates before 1987 Recipients of blood transfusions or donated organs before July 1992 Previous dialysis patients (HCV RNA in addition to HCV Ab) Children born to infected mothers (test after 18 months of age) Patients with signs or symptoms of liver disease (e.g., abnormal transaminases) Donors of blood, plasma, organs, tissues, or semen
Yearly Testing	People who currently inject drugs Long-term hemodialysis patients HIV-infected patients (HCV RNA in addition to HCV Ab)

Table 2 CLASSES OF DIRECT-ACTING ANTIVIRALS

Drug Name	Protease Inhibitor	NS5A Inhibitor	Polymerase Inhibitor
Boceprevir	X		
Telaprevir	X		
Simeprevir	X		
Asunaprevir	X		
Paritaprevir	X		
Sofosbuvir			X (nucleotide)
Dasabuvir			X (nonnucleotide)
Ledipasvir		X	
Daclatasvir		X	
Ombitasvir		X	

Courtesy Dr. Khungar and Dr. Reddy

Table 3

TREATMENT REGIMENS FOR TREATMENT NAÏVE PATIENTS

Genotype	Regimen	Treatment Duration	Studies	SVR (%)
1a	1. LDV (90 mg)/SOF (400 mg) 2. Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV 3. SOF (400 mg)/SIM (150 mg) with or without weight-based RBV	1. 12 weeks or 8 weeks if RNA<6 million IU/mL 2. 12 weeks or 24 weeks (C) 3. 12 weeks or 24 weeks (C)	1. ION-1, ION-3 2. SAPPHIRE-1, PEARL-IV, TURQUOISE-II 3. COSMOS	1. 97-99 2. 95-97, 89-95 (C) 3. 95-100, 79-86 (C)
1b	1. LDV (90 mg)/SOF (400 mg) 2. Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg). Add RBV if cirrhotic. 3. SOF (400 mg)/SIM (150 mg)	1. 12 weeks or 8 weeks if RNA<6 million IU/mL 2. 12 weeks 3. 12 weeks or 24 weeks (C)	1. ION-I, ION-3 2. SAPPHIRE-1, PEARL-III, TURQUOISE-II 3. COSMOS	1. 97-99 2. 98-100 3. >90
2	1. SOF (400 mg) and weight-based RBV	1. 12 weeks or 16 weeks (C)	1. FISSION, POSITRON, VALENCE	1. 94
3	1. SOF (400 mg) and weight-based RBV 2. SOF (400 mg) and weight-based RBV plus weekly PEG-IFN for IFN-eligible	1. 24 weeks 2. 12 weeks	1. FISSION, POSITRON, VALENCE 2. PROTON, ELECTRON	1. 84-92 2. 97
4	1. LDV (90 mg)/SOF (400 mg) 2. Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV 3. SOF (400 mg) and weight-based RBV 4. SOF (400 mg) and weight-based RBV plus weekly PEG-IFN 5. SOF (400 mg)/SIM(150 mg) with or without weight-based RBV	1. 12 weeks 2. 12 weeks 3. 24 weeks 4. 12 weeks 5. 12 weeks	1. SYNERGY 2. PEARL-I 3. Ruane 2014 4. NEUTRINO 5. RESTORE	1. 95-100 2. 95-100 3. 92 4. 96 5. 83
5	1. SOF (400 mg) and weight-based RBV plus weekly PEG-IFN 2. Weekly PEG-IFN plus weight-based RBV for 48 weeks	1. 12 weeks 2. 48 weeks	NEUTRINO	100
6	1. LDV (90 mg)/SOF (400 mg) 2. SOF (400 mg) and weight-based RBV plus weekly PEG-IFN	1. 12 weeks 2. 12 weeks	1. NCT01826981 2. NEUTRINO	1. 96 2. 100

Courtesy Dr. Khungar and Dr. Reddy

C = cirrhosis, LDV = ledipasvir, SOF = sofosbuvir, SIM = simeprevir, RBV = ribavirin

beta-adrenoreceptor agonist salmeterol (causing QT prolongation).

Choices of regimens

Four factors should be considered when considering treatment for HCV infection: genotype (including subtype 1a or 1b for genotype 1 patients), prior treatment experience, the presence or absence of cirrhosis, and decompensations from cirrhosis if present. Approved regimens are listed in Tables 3[11-25], 4[26-31], and 5[32,33].

These tables provide the essence of what practicing gastroenterologists/hepatologists need to know, including genotype-specific regimens, treatment duration, the studies that provide evidence for the recommendation, and expected SVR rates. Many physicians feel overwhelmed by the sheer volume of data on new regimens and this article aims to condense the most essential information for easier use and incorporation into your practice.

Clinical pearls from recent studies

New data suggest that 10%-15% of patients with genotype 1 infection treated with simeprevir and sofosbuvir will experience treatment failure with relapse after stopping therapy. Failure is more common in genotype 1a and patients with cirrhosis. Data from the COSMOS study indicate that treatment failure is associated with resistance to simeprevir with cross-resistance to other NS3/4A protease inhibitors such as paritaprevir, telaprevir, and boceprevir. Sofosbuvir resistance-associated variants were not observed in the COSMOS trial and are rare in clinical practice. Retreatment with sofosbuvir/ledipasvir in those who relapsed on sofosbuvir/ribavirin is noted to have high SVR rates.[34]

For most patients, baseline RNA levels do not influence treatment choice or duration. With ledipasvir/sofosbuvir, post-hoc analysis from the ION-3 trial in treatment-naive patients without cirrhosis showed that those with an HCV RNA level of less than 6 million IU/mL had similar relapse

Continues on page 12

Table 4

TREATMENT REGIMENS FOR TREATMENT EXPERIENCED PATIENTS

Genotype	Regimen	Treatment Duration	Studies	SVR (%)
1a	1. LDV (90 mg)/SOF (400 mg) (including prior protease inhibitor failures)	1. 12 weeks, 24 weeks (C)	1. ION-2	1. 94
	2. Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (only in those who failed PEG-IFN and RBV and not including a protease inhibitor)	2. 12 weeks, 24 weeks (C)	2. SAPPHIRE-II, TURQUOISE-II	2. 96
	3. SOF (400 mg) plus SIM (150 mg) with or without weight-based RBV (only in those who failed PEG-IFN and RBV and not including a protease inhibitor)	3. 12 weeks, 24 weeks (C)	3. COSMOS	3. 93-96
	4. LDV (90 mg)/SOF (400 mg) plus weight-based RBV	4. 12 weeks	4. SIRIUS	4. 96-97
1b	1. LDV (90 mg)/SOF(400 mg) (including prior protease inhibitor failures)	1. 12 weeks, 24 weeks (C)	1. ION-2	1. 94
	2. Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg), weight-based RBV in cirrhosis(see above)	2. 12 weeks, 12 weeks (C)	2. PEARL-II, TURQUOISE-II	2. 96-100
	3. SOF (400 mg) /SIM (150 mg) (see above)	3. 12 weeks, 24 weeks (C)	3. COSMOS	3. 93-96
	4. LDV (90 mg)/SOF (400 mg) plus weight-based RBV	4. 12 weeks (PI failure)	4. SIRIUS	4. 96-97
2	1. SOF (400 mg) and weight-based RBV	1. 12 weeks, 16 weeks (C)	1. VALENCE, FUSION	1. 60-88
	2. SOF (400 mg) and weight-based RBV, PEG-IFN	2. 12 weeks	2. LONESTAR-2	2. 93-100
3	1. SOF (400 mg) and weight based RBV	1. 24 weeks	1. VALENCE, FUSION	1. 79
	2. SOF (400 mg) and weight based RBV plus weekly PEG-IFN	2. 12 weeks	2. LONESTAR-2	2. 83
4	1. LDV (90 mg)/SOF (400 mg) for 12 weeks	1. 12 weeks	1. SYNERGY	1. 95
	2. Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV	2. 12 weeks	2. PEARL-1	2. 100
	3. SOF (400 mg) and weight-based RBV plus weekly PEG-IFN	3. 12 weeks	3. NEUTRINO	1. 96
	4. SOF (400 mg) and weight-based RBV	4. 24 weeks	4. Esmat 2014	2. 89
5	1. SOF (400 mg) and weight-based RBV plus weekly PEG-IFN	1. 12 weeks	NEUTRINO	100
	2. Weekly PEG-IFN plus weight-based RBV	2. 48 weeks		
6	1. LDV (90 mg)/SOF (400 mg)	1. 12 weeks	1. NCT01826981	1. 96
	2. SOF (400 mg) and weight-based RBV plus weekly PEG-IFN	2. 12 weeks	2. NEUTRINO	2. 100

Courtesy Dr. Khungar and Dr. Reddy

C = cirrhosis, LDV = ledipasvir, SOF = sofosbuvir, SIM = simeprevir, RBV = ribavirin

Continued from page 11

rates with 8 or 12 weeks of therapy.

Patients with genotype 1a tend to have higher relapse rates than those with genotype 1b with certain regimens, so if the subtype is not known, the patient should be treated as having genotype 1a.

Rarely, a patient may show the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data are sparse and unless advanced fibrosis is present, it would be prudent to wait for pangenotypic treatment in these cases.

Special populations

For patients with creatinine clearance > 30 mL/min, no dose adjustments of sofosbuvir, simeprevir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir/dasabuvir are needed. For those with creatinine clearance < 30 mL/min and those on hemodialysis, safety and efficacy data are not yet available. The post–liver transplant population should be handled by a transplant hepatologist (preferably at the center where the patient had their surgery). Additionally, with the advent of the new DAA therapies, treatment of the HIV co-infected population has become far less challenging than in the past. The most important point to remember is that HIV/HCV co-infected patients should be treated and retreated the same as people without HIV infection, after recognizing and managing interactions with antiretroviral medications. Drug-drug interactions are of diminishing concern with sofosbuvir-based regimens, while ritonavir-boosted protease inhibitor regimens present some challenges. If changes in an antiretroviral drug regimen are planned, this should be done in collaboration with the HIV provider.

Future of HCV treatment, potential research opportunities

Improved treatments for HCV involve shorter durations of therapy with robust pangenotype DAAs, mostly interferon-free regimens, and fewer side effects. Very extensive guidelines are available with continued

updates due to the rapidly evolving therapies (condensed here for your review). The main obstacle to an attainable cure for patients is the cost of therapy. Applying the principles of distributive justice, stratification, and prioritization of patients on the basis of disease stage and potential gain from treatment is necessary. Prices will likely continue to drop as more drugs are developed and treatment may evolve to even shorter courses of therapy. An obstacle to treatment from a provider's perspective is inadequate screening and referral.

The CDC recommendations and improved knowledge of HCV have already improved screening tremendously, but more widespread programs to identify and refer HCV patients need to be implemented. Treatments appropriate for patients with end-stage renal disease need to be developed. Broader-scale public health efforts need to be implemented to ensure access to DAAs for patients in countries with limited resources. Many of the registration trials included small numbers of patients.

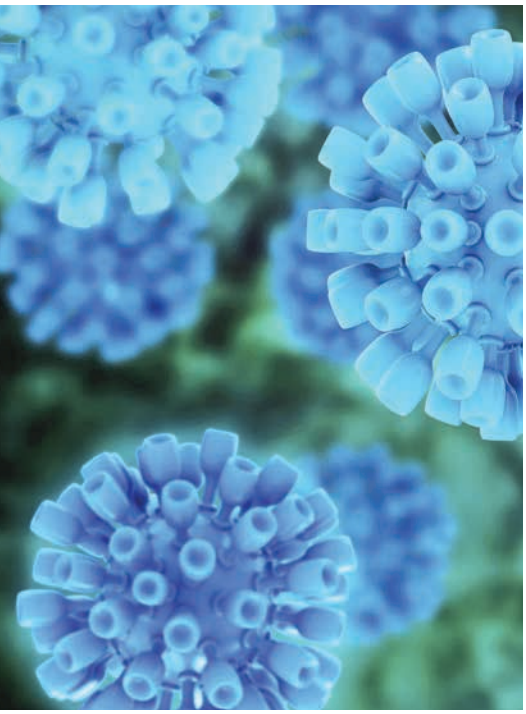

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Table 5 TREATMENT REGIMENS FOR PATIENTS WITH DECOMPENSATED CIRRHOSIS

Genotype	Regimen	Treatment Duration	Studies	SVR (%)
1 and 4	LDV (90 mg)/SOF (400 mg)/RBV (started at 600 mg)	a. 12 weeks b. 24 weeks (SOF failure)	a. SOLAR-1 b. SOLAR-1	a. 86-87 b. 89-90
2 and 3	SOF (400 mg)/weight-based RBV	Up to 48 weeks	Curry 2014	91

LDV = ledipasvir, SOF = sofosbuvir, RBV = ribavirin

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Further study into the real-world response to the new DAAs will need to be conducted, as with the observational HCV TARGET study, to determine pitfalls of therapy when applied to larger, sometimes less ideal patient populations. Treatment is only one aspect of eradicating hepatitis C. As with any communicable disease, vaccination will be a crucial step in this process and research to develop a vaccine will be essential in the next few years. ■

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The Answer

From ***What's Your Diagnosis?*** on page 7

Computed tomography enterography shows the transverse colon and lateral segment of the left hepatic lobe herniating into the thoracic cavity, which are consistent with a diagnosis of Morgagni's hernia. Figure A shows a coronal image of the transverse colon and left hepatic lobe herniating into the thoracic cavity, whereas Figure B shows the same findings in sagittal section. Figure C shows an axial image of the transverse colon in the anterior thorax. Figure D shows an axial image, which contains both the edge of the liver as well as transverse colon in the anterior thorax.

Morgagni's hernia is a type of congenital diaphragmatic hernia that results from defects of the anterior diaphragm. It is rare, comprising only 2%–3% of congenital diaphragmatic hernia cases.[1] The hernia usually contains omentum and transverse colon; however, the liver (as in our patient) or stomach can also be contained in the hernia sac. As in this patient, most Morgagni's hernias (80%–90%) are located on the right side of the thorax.[2] They are usually identified on chest radiography, often on lateral imaging because of the anterior location of the hernia, although computed tomography and barium radiography are more sensitive and can be used to confirm the diagnosis.[3] Morgagni's hernias are frequently asymptomatic, especially in adults. Those who become symptomatic may present with abdominal pain owing to viscera strangulation, chest discomfort, or with respiratory symptoms such as dyspnea. Treatment can include laparoscopic or thoracoscopic reduction as well as laparotomy, with the type of surgery chosen depending on the acuity of the presentation and individual patient characteristics. Surgery is usually recommended, even in asymptomatic individuals, given the risk of incarceration and subsequent obstruction and/or ischemia.[3] Conservative measures of watchful waiting can be considered in those who are asymptomatic with multiple medical comorbidities or advanced age.

The patient was referred to thoracic surgery for further evaluation. He refused operative intervention and currently remains asymptomatic. ■

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Snapshots from the AGA Journals

ID of Subtypes, Mutations in CRC Increases Survival

January Gastroenterology (doi:10.1053/j.gastro.2014.09.038 and doi:10.1053/j.gastro.2014.09.041)

Key clinical point: Genetic factors in colon cancer determine long-term prognosis, but tumors are heterogeneous and the factors are complex.

Major finding: Tumors with the least favorable prognosis in both studies were serrated and DNA mismatch-repair proficient and positive for a BRAF mutation. Tumors with deficient MMR (MSI-H), whether sporadic or associated with Lynch syndrome, consistently exhibited the most favorable prognosis and highest rates of long-term survival.

Data source: Tumor material from the North Central Cancer Treatment Group adjuvant chemotherapy trial was analyzed and Cox regression models were used to estimate hazard ratios, 95% confidence intervals, and associations for each subtype with specific diseases and overall mortality, all of which were adjusted for age, sex, body mass, diagnosis year, and smoking history.

Disclosures: The investigators for both studies reported no relevant financial disclosures.

Commentary

Dr. Daniel C. Chung is associate professor, department of medicine, Harvard Medical School, Boston, and director, Hi-Risk Gastrointestinal Cancer Clinic, Massachusetts General Hospital, also in Boston. He has no conflicts of interest.

It is now recognized that colon cancer is quite heterogeneous on a genetic level, and the clinical features associated with each of these genetic subtypes are equally heterogeneous. The two current studies addressed the question of whether long-term prognosis differs among these genetic subtypes. Colon tumors were first divided into five distinct categories, based upon a panel of multiple molecular markers. One study analyzed more than 2,700 colon cancers of all stages, whereas the other examined more than 2,700 stage III tumors from a North Central Cancer Treatment Group adjuvant chemotherapy trial.

Similar patterns emerged. Tumors with the least favorable prognosis were the so-called "serrated" tumors that are DNA mismatch-repair (MMR) proficient and are positive for a BRAF mutation. Tumors with deficient MMR (MSI-H), whether sporadic or associated with Lynch syndrome, consistently exhibited the most favorable prognosis and highest rates of long-term survival.

These studies provide strong evidence that links survival with specific tumor genotypes, regardless of stage or treatment, and establish the significance of molecular genotyping for prognostic purposes. There are other important reasons to perform tumor genotyping, including the identification of unrecognized Lynch syndrome. However, the therapeutic implications of tumor genotyping remain less clear, as meaningful targeted therapies for each of the specific subgroups are still lacking. In particular, effective targeting of the BRAF oncogene in serrated tumors remains an important priority. More refined molecular classifications are likely to emerge in the future, and the opportunities to offer more precise and personalized approaches to management should increase in parallel. ■

Stress Independently Predicts Peptic Ulcers

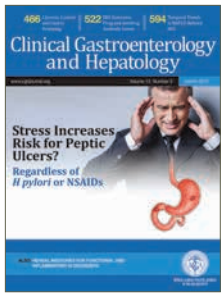
March Clinical Gastroenterology and Hepatology [doi:10.1016/j.cgh.2014.07.052])

Key clinical point: High stress levels independently predicted peptic ulcers.

Major finding: After adjustment for other risk factors, every one-point increase on a 12-item stress questionnaire increased the odds of peptic ulcers by 12% (OR, 1.12; 95% CI, 1.01-1.23).

Data source: Prospective, population-based study of 76 patients with peptic ulcers in Denmark.

Disclosures: The Kirby Family Foundation funded the statistical analysis. The researchers reported no conflicts of interest.



Commentary

Dr. Nimish Vakil, AGAF, FASGE, FACP, is a physician specializing in gastroenterology at the Aurora Wilkinson Medical Clinic in Summit, Wisc. He is a consultant for Astra Zeneca, Ironwood, and Baxter Pharmaceuticals.

Stress was the most frequently cited cause of ulcer disease before *Helicobacter pylori* was discovered. The harried executive who developed an ulcer was a widely accepted profile of an ulcer diathesis. When the role of *H. pylori* infection and NSAIDs became clear, the role of stress was downplayed and some articles and textbooks dismissed stress as a potential cause for ulcer disease.

Studies of New York City residents suggest a higher incidence of ulcer disease after the Sept. 11 attacks and studies from Japan have shown an increase in the incidence of ulcer disease after the nuclear reactor disaster. In this issue of *Clinical Gastroenterology and Hepatology*, Dr. Levenstein and her colleagues report the results of a study of stress and the incidence of ulcer disease in Danish subjects. In 1982-1983, a population-based study in Denmark collected sera and psychological data in over 3,000 subjects and reinterviewed them in 1987-1988 and 1993-1994. An ad-hoc, unvalidated scale developed by the authors measured stress. It included a psychological scale used by the Danish military to identify recruits unsuitable for military service but also included tranquilizer use, working more than 40 hours/week, and unemployment. In a multivariate analysis, they found that stress increased the risk for both gastric and duodenal ulcers, with an adjusted odds ratio of 1.19 per point increase in the stress scale for gastric ulcers (95% confidence interval, 1.03-1.37) and a odds ratio of 1.1 per point increase in the stress index for duodenal ulcers (95% CI, 0.98-1.27).

There are obvious limitations with this study: a historical cohort, an unvalidated stress scale, the inclusion of items that may not represent stress in some cultures (e.g., working more than 40 hours/week), and the lower bound of confidence intervals for risk which are very close to one. However, studies such as this tell us that we have been too quick to dismiss the role of stress in ulcer pathogenesis. With declining *H. pylori* prevalence and the development of safer NSAIDs, stress will undergo a renaissance in the pathogenesis of ulcer disease. ■

H. pylori Might Help Regulate Gastric Immunity

March Cellular and Molecular Gastroenterology and Hepatology [http://dx.doi.org/10.1016/j.jcmgh.2014.12.003 5])

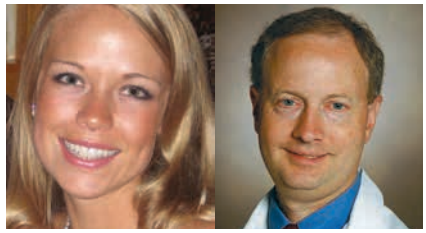
Key clinical point: *H. pylori* may help regulate gastric immunity in some circumstances.

Major finding: Chronic gastric *H. pylori* infection lowered expression of IL-33, a cytokine that helps activate the CD4+ T helper cell 2 response. This may tilt the immune response toward T helper cell 1 response, which can trigger precancerous changes.

Data source: Immunofluorescence, flow cytometry, and quantitative real-time polymerase chain reaction studies of tissue specimens from humans and mice.

Disclosures: The study was funded by the Victorian Government's Operational Infrastructure Support Program and NH&MRC Australia. The researchers reported no conflicts of interest.

Commentary



Jennifer M. Noto, Ph.D., and Richard M. Peek Jr., M.D., of the department of medicine, division of gastroenterology, hepatology, and department of nutrition and cancer biology, Vanderbilt University, Nashville, Tenn. They have no conflict of interest. They acknowledge the following funding sources: NIH R01CA077955, R01DK058587, P01CA116087, and P30DK058404.

Gastric adenocarcinoma is the second leading cause of cancer-related death worldwide, and chronic infection with *Helicobacter pylori* is the strongest known risk factor for the development of this malignancy. *H. pylori* colonization rates hover around 80%-90% in developing countries, but only a fraction of infected individuals ever develop disease. It is increasingly apparent that gastric carcinogenesis is multifactorial, influenced by host responses, *H. pylori* virulence properties, and environmental cofactors. Parasitic helminth infections among *H. pylori*–infected individuals have been associated with a lower risk for the development of gastric cancer, and experimental data from animal models of *Helicobacter* infection have demonstrated that concurrent helminth infection attenuates the vigor of the host immune response and reduces gastric atrophy. Infection with *H. pylori* typically induces a Th1-polarized immune response, while helminths drive Th2 responses. Concurrent infections with helminths is endemic in regions of some developing countries that have a high prevalence of *H. pylori* infection, but a lower than expected rate of gastric cancer. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Buzzelli et al. provide fresh insights into the role that IL-33 plays in polarizing Th2 immune responses by demonstrating that chronic, but not acute, *H. pylori* infection suppresses IL-33, which ultimately leads to a predominant Th1 response. These findings may represent a novel mechanism (e.g., manipulation of IL-33) explaining why populations harboring concurrent helminth and *H. pylori* infection have a reduced risk of gastric cancer. ■

Postfellowship Pathways: Advanced Endoscopy Fellowship

By Brintha K. Enestvedt, M.D., MBA

Brintha Enestvedt is currently assistant professor at Oregon Health Science University. She completed her advanced endoscopy fellowship at the University of Pennsylvania and her GI fellowship at Oregon Health Science University. Dr. Enestvedt can be reached at enestveb@ohsu.edu.

What type of advanced endoscopy fellowships are available? The United States has approximately 65 advanced endoscopy fellowship (AEF) programs and as of 2013, there were 14 in Canada. There are many expert advanced endoscopists outside the United States as well; if you are interested in pursuing an international experience, I recommend that you speak with your mentors to identify and contact a leader in a country that meets your needs.

AEF programs vary in the number of fellows that are trained yearly, the number of faculty that contribute to the training, the yearly volume of procedures, duration of training, number of hospitals you are expected to cover, and the breadth of procedural exposure as well as the amount of general GI clinical service time a fellow is required to perform during their AEF training. There is much more to an advanced endoscopy fellowship than procedural training; an equally important component is the opportunity to learn the indications, contraindications, risks, limitations, and adverse events associated with each procedure. Furthermore, one can develop the knowledge base necessary to know when not to perform a procedure because it is unlikely to benefit the patient. All of these variables should play a role in the fellow's decision about a program and, as such, there are several important questions to ask during the interview process:

- What has the endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) volume been for the fellows that have graduated in the last 5 years?
- Does your fellowship provide training in EUS alone, ERCP alone, a combination, or does it include experience in other advanced techniques that may include luminal stenting, endoscopic mucosal resection, deep enteroscopy (single, spiral, or double balloon enteroscopy), etc.?
- What types of jobs have fellows graduating from the program accepted?
- Are the fellows performing the majority of each procedure, at least by the end of their training?
- What other commitments will a fellow have during his or her advanced training?
- What are the expectations for research endeavors during the advanced endoscopy year?

What does the advanced endoscopy fellowship application process entail?

The first step is deciding that you want to pursue advanced training.

This important step requires due diligence, and I recommend speaking with as many trainees and current practitioners at as many different points in their careers as possible to get a clear sense of what their daily lives are like.

Once you've decided to pursue advanced training in endoscopy, the American Society for Gastrointestinal Endoscopy (ASGE) will match you with an appropriate program (www.asgematch.com). Applicants are able to access the match website in early December and complete their application by March. Interviews occur from March to May and rank lists are due at the end of June. Match day is in the middle of July with accepted applicants starting their AEF training 1 year later. The match website also provides important information about each program, including the number of fellows accepted per year, the program director, etc.

What led you to pursue an advanced endoscopy fellowship?

The faculty members that influenced me the most during my training were advanced endoscopists. What I admired most about their practice was their unique ability to offer patients a variety of procedures, all of which were in their armamentarium. I personally wanted to be able to assess a patient and offer them any procedure they needed. Being able to provide the totality of endoscopic care and the tenacious attitude inherent in most advanced endoscopists was in line with my interests and personality. Additionally, some of the interactions I enjoyed the most during my general fellowship were those with our surgeons and radiologists. Advanced endoscopy is a marriage among all of these fields, including oncology and pathology, and I found that my understanding of any disease was greatly enhanced when discussed and managed in a multidisciplinary fashion.

Many fellows lament having to observe procedures during their advanced endoscopy fellowship rather than having their hands on the scope. This is inevitable.

What was the most challenging aspect of your advanced endoscopy fellowship?

An advanced endoscopy fellowship is no doubt challenging in a multitude of ways. The learning curve is steep; the hours are long; the cases are intense; the procedural stakes are often high; there are numerous minute details about tools you need to commit to memory; your confidence wavers on a daily basis; and all while you are trying your best to get the job done and not disappoint the mentor standing behind you. The aspect I found to be most challenging ended up being a great asset to me, though I didn't recognize it at the time. I trained with five different attendings, each with their own unique ERCP technique and endoscopy styles. As the year progressed, I was frequently frustrated because I felt I had not improved at the pace I initially expected. I now realize that that this was a product of performing the same procedure in multiple different ways and not having a standard technical approach to each case. I am so fortunate that now

Continues on page 20

Courtesy Dr. Brintha K. Enestvedt

Dr. Brintha K. Enestvedt and endoscopy technician David Artherton.

Because so much of advanced endoscopy centers on cancer care, you have to be comfortable with the fact that the majority of your patients have cancer and you should enjoy being part of a multidisciplinary team taking care of these patients.

Continued from page 19

in my practice, when I encounter a difficult cannulation or challenging stricture for example, I have at least five different ways to approach the procedure, making me well equipped for a successful technical outcome.

Many fellows lament having to observe procedures during their advanced endoscopy fellowship rather than having their hands on the scope. This is inevitable. I encourage fellows to appreciate how much there is to be gained by simply watching a skilled endoscopist during a procedure. When your attending has the scope, take the opportunity to figure out what makes them successful. Observe what they are doing with their body position. What is the position of their hands and fingers in relationship to the catheter? What is the technician doing and why? If you are not performing the procedure, ask to perform the GI technician's duties. This gives you a much deeper understanding of the procedure, technique, and tools and allows you to determine what makes a helpful technician.

How has your advanced endoscopy fellowship benefited your career?

I am currently practicing in an academic medical center. My advanced endoscopic training has offered me the opportunity to help take care of some of our most complicated patients. It has afforded me the privilege to serve as a consultant to other gastroenterologists who wish to discuss challenging and interesting patients. Importantly, during my fellowship I had the opportunity to meet and learn from some of the most skilled endoscopists and clinicians. My relationship with them and other mentors spurred my interest in committee work through GI professional societies, which in turn helped me develop a strong network of friends and colleagues across the country who share my same fervor for advanced endoscopy, and on whom I can rely upon for support and guidance.

Do you think an advanced endoscopy fellowship is necessary for young gastroenterologists who want to effectively incorporate ERCP and EUS into their practice?

I am a firm believer in advanced training for these procedures, as they carry higher risk for adverse events than standard esophagogastroduodenoscopy (EGD) and colonoscopy. Moreover, as the field of advanced endoscopy evolves, we are doing more technically complicated procedures that toe the line of minimally invasive surgery. Not only does an advanced endoscopist need to be able to perform the procedure, but also be able to expeditiously recognize, manage, or even preempt adverse events. I believe that an intense year of dedicated training is necessary in order to gain exposure to the wide array of disease processes you will eventually care for as well as equip you with the tools and techniques to manage these medical problems. Maintaining your skills after fellowship is incredibly important and this means having the appropriate volume of procedures yearly. To that end, the first year after fellowship is critical in terms of achieving the necessary volume to solidify your skills. Additionally, it is important to evaluate the current job market, as you need to seriously consider if there will be a need for your newly acquired skills where you will practice.

What qualities are important for a career in advanced endoscopy?

Because so much of advanced endoscopy centers on cancer care, you have to be comfortable with the fact that the majority of your patients have cancer and you should enjoy being part of a multidisciplinary team taking care of these patients. This can be, at times, emotionally exhausting and far more technically challenging than general GI procedures. As I previously mentioned, given the complexity of cases and the severity of illness of your patients, you have to be persistent and determined in order to achieve technical and clinical success. To this end, advanced endoscopy requires intensive preprocedure planning as well as multiple back-up plans should your initial strategies not pan

out. Effective communication is key – oftentimes, the advanced endoscopist is the first person to tell a patient they have cancer. Qualities of compassion and empathy are essential in all aspects of medicine but are particularly important during these critical conversations. Finally, after a procedure, communication with the patient's oncologist, surgeon, radiation oncologist, or primary care doctor to discuss next steps in management occupies a considerable amount of time.

What can fellows do during their training to best prepare for a future advanced endoscopy fellowship?

Once you are committed to an AEF, I would spend as much time as possible with an advanced endoscopist at your institution, even if it means just observing procedures. Many techniques are repetitive and gaining a general understanding of the available tools and tactics can help you strategize prior to a procedure. Get to know your endoscopy technician well; watch them do their job, and ask them questions about how things work. It will greatly contribute to your understanding of why an attending chooses a specific tool or technique. Do as many general GI procedures as you can; the better your general endoscopic skills are, the more likely your mentors will be to allot you more scope time. Think about a research project and start planning it ahead of time, even before you start your AEF year. It can be hard to start and complete a project during such an intense year, but it is much easier to work on something that you have already started. Additionally, pass a side-viewing duodenoscope or EUS scope as many times as you can into the duodenum. While prior experience in EUS or ERCP is ***not*** necessary for an advanced fellowship, these basic endoscopic skills certainly help your confidence early on and allow you to focus on the next set of skills you want to acquire. Finally, look at as many CT scans and MRIs as you can to become more familiar with cross-sectional anatomy and also consider attending a tumor board conference at your institution. ■

Acknowledgements: Gene Bakis, Nisa Kubiliun, Vinay Chandrasekhara, M. Brian Fennerty

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QUESTIONS

// Answers on page 25

Q1: Constipation is more common after which of the following bariatric surgical procedures?

A. Roux-en-Y gastric bypass
B. Gastric banding
C. Biliopancreatic diversion
D. Vertical-banded gastroplasty
E. Sleeve gastrectomy

Q2: A 44-year-old female with a history of short bowel syndrome presents to the office with complaints of a scaly red rash on her face, groin, and hands and progressive alopecia. What is the most likely etiology?

A. Vitamin B_{12} deficiency
B. Zinc deficiency
C. Vitamin D deficiency
D. Copper deficiency
E. Vitamin E deficiency

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A Personal Story

By Akwi W. Asombang, M.D.

Dr. Asombang is associate professor of clinical medicine in the division of gastroenterology/hepatology at the University of Missouri–Columbia School of Medicine. She completed a combined internal medicine–pediatric residency at Saint Louis University School of Medicine/Cardinal Glennon Children's Hospital and an adult gastroenterology/hepatology fellowship at Washington University School of Medicine, St. Louis.

When I completed my residency, my goal was to pursue a combined adult-pediatric gastroenterology fellowship and ultimately contribute to both medical education and patient care in Zambia, my home.

During my first year of gastroenterology fellowship, I had the opportunity to apply to the National Institutes of Health Fogarty International Clinical Research Fellowship (NIH FICRF). I submitted the application during the sixth month of my fellowship and was awarded a grant by the end of the year. I built a team of mentors and collaborators based in Zambia and the United States (including Washington University in St. Louis and Fogarty mentors from Vanderilt University in Nashville), whom I can credit for contributing to the success of my work.

Prior to traveling to Zambia, as part of the FICRF program, I attended the 2-week orientation at the NIH campus in Bethesda, Md. This orientation provided information regarding the conduct of research in low- to middle-income countries (LMICs) and an opportunity to meet other fellows and scholars in the Fogarty program.

Zambia is in southern Africa and has a population of about 14 million. I had the joy of conducting my research at the University Teaching Hospital in the capital city, Lusaka. The University Teaching Hospital is the largest tertiary academic center in Zambia, with approximately 1,600 adult beds and 400 pediatric beds. The endoscopy unit provides both inpatient and outpatient general GI services. It is usually staffed by two to three nurses, one gastroenterologist, one internal medicine endoscopist, one pediatric gastroenterologist, and two surgical endoscopists.

My research in Zambia focused on the role of diet as a risk factor for gastric cancer, specifically measuring urinary isoprostanes as a marker of oxidative stress. While conducting this research, our team also observed that a significant number of patients diagnosed with esophageal cancer were younger than 45 years of age, a finding so far without explanation. We extended our study to examine risk factors related to the etiology of esophageal cancer. We presented our work related to both gastric/esophageal cancer at international meetings (DDW, ACG, UEGW) and published in various scientific journals.[1-4]

The University Teaching Hospital is the largest tertiary academic center in Zambia, with approximately 1,600 adult beds and 400 pediatric beds.

COURTESY DR. ASOMBANG

L to R: Dr. Carla Chibwesha (University of Alabama at Birmingham), Dr. Kondwelani Mateyo (University of Zambia School of Medicine), Dr Linnaea Schuttner (University of Washington), Dr. Omar Siddiqi (Beth Israel Deaconess Medical Center), Dr. Akwi W. Asombang (Washington University School of Medicine), Dr. Katherine Cherry Liu (University of Alabama at Birmingham).

My workdays started by 7 a.m. and ended between 5 and 6 p.m. I spent almost every day in the endoscopy unit performing procedures, except on Thursdays, which I spent following up pathology results, processing samples, recruiting patients, entering data, meeting with collaborators, or visiting inpatients. Tuesday afternoons were generally spent seeing patients in the clinic.

The health care providers in the clinic performed upper endoscopies almost daily (except on Thursdays, unless urgent), and colonoscopies on Thursdays. I saw numerous pathologic endoscopic findings including gastric ulcers, esophageal varices, gastric Kaposi sarcoma–related lesions, caustic ingestion injuries, and gastric and esophageal cancers. We evaluated a variety of ailments in the clinic including gastroesophageal reflux disease, abdominal pain, irritable bowel syndrome, inflammatory bowel disease (ulcerative colitis, Crohn's disease), hepatitis (autoimmune and

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Patient care in Zambia is very family oriented, with both patients and families expressing appreciation for health care providers.

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hepatitis B), diarrhea, GI cancers, and schistosomiasis with esophageal varices.

One of my saddest experiences in Zambia was when we diagnosed a 19-year-old girl with rectal signet ring cell adenocarcinoma.[5] I maintained communication with her until she succumbed to the disease almost a year later and I remain in contact with her family. This experience highlights the important epidemiological differences of gastrointestinal cancers in an LMIC, such as Zambia, compared with western countries and highlights the urgent need for further studies that explain epidemiology, management, and outcomes in these disorders.

One of the more positive experiences I had in Zambia was working with the local team to host the first gastroenterology/hepatology workshop, which attracted attendees from neighboring countries Malawi, Zimbabwe, and the Democratic Republic of Congo as well as speakers from England.[6]

One of the main challenges of working and conducting research in Zambia was the limited laboratory consumables needed to conduct our research. The host laboratory would run out of reagents needed for the day-to-day routine diagnostics. We eventually had to rebudget in order to restock the supplies. This lack of resources is likely present in other LMICs as well. But the strengths of working in Zambia are many: the opportunities to contribute to the knowledge gaps regarding gastrointestinal cancers and other GI diseases, the potential to raise awareness among other providers about gastrointestinal ailments, and the ability to build partnerships and collaborations. My time in Zambia was predominantly focused on clinical research; however, I was also involved with routine patient care. I enjoyed working with patients, both from a clinical and research perspective. Patient care in Zambia is very family oriented, with both patients and families expressing appreciation for health care providers.

I believe our research team had a positive impact on the community by providing care even for patients who were not enrolled in the study, providing histopathology results sooner, and expediting care with a multidisciplinary approach.

I was struck by the enthusiasm and work ethic of the nurses; with at least 10-15 procedures per day between the two or three nurses, they were responsible for registering

Courtesy Akwi Asombang

Dr. Asombang with her nephew Noah Imani Bahati in Livingstone, Zambia.

patients upon arrival, assisting during the procedure, monitoring patients after the procedure, cleaning the instruments, and setting up the room for the next procedure.

My experience in Zambia strengthened my interest in pursuing a career in global health, focused on teaching and providing patient care in sub-Saharan Africa. With the increase in noncommunicable diseases (NCDs) such as cancers, there is a need for subspecialists such as a gastroenterologist with advanced endoscopic skills. This increase in NCDs has been attributed to heightened rates of physical inactivity, urbanization, and unhealthy dietary habits. Practitioners in our field have to understand and look beyond communicable diseases as the predominant cause of mortality and morbidity in Africa as well as accept the necessary role of gastroenterologists and endoscopy in patient care.

I chose Zambia as a site for research because it is my home and my career intentions are to have a joint appointment both in the United States and Zambia that allows me to remain engaged in gastroenterology. I have maintained contact with some of my collaborators and plan more joint work in the future. I also plan to return to Zambia to conduct research analyzing pancreatic cancer by using the Cancer Disease Hospital database.

My recommendation to medical students, residents, and fellows interested in global health is to take the opportunity while in training. Opportunities do not end as a trainee but carry on throughout one's career. But perhaps most importantly, I was finally home with my family and making a positive impact on patient care.

I thank my mentors and supervisors for their guidance and support in making this an exciting and productive experience: Fogarty (Dr. Sten Vermund, Dr. Douglas Heimberger), Washington University in St. Louis (Dr. Nicholas Davidson, Dr. Prakash Gyawali, and Dr. Deborah Rubin), and Dr. Paul Kelly. I thank the Zambian physicians with whom I worked on this project and look forward to continued collaborative opportunities. ■

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ANSWERS

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QI: ANSWER: B

CRITIQUE

Constipation occurs in up to 39% of patients who undergo gastric banding. Diarrhea occurs in 46% of patients after Roux-en-Y gastric bypass and in 55% of patients after biliopancreatic diversion. Neither vertical-banded gastroplasty nor sleeve gastrectomy is associated with a significant change in bowel habits.

Reference

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Q2: ANSWER: B

CRITIQUE

Zinc deficiency can occur with short gut syndrome due to malabsorption. It is characterized by alopecia, loss of taste, poor wound healing, and scaly rash similar to acrodermatitis enteropathica, which can be seen among patients who have an autosomal recessive disorder of zinc metabolism.

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Protecting Your Future: A Discussion About Disability Insurance for GIs

By Jay Weinberg, CLU, ChFC

Mr. Weinberg is a financial planner with Atlantic Pension Planning Corp. whose practice primarily assists physicians and dentists. Mr. Weinberg can be reached at jay@atlanticpension.com.

Who needs disability insurance?
Physicians who want to protect their most valuable asset – the ability to earn money – and don't have several million dollars in liquid assets, or friends or family who can provide financial support for the next 30–40 years, should consider procuring disability insurance.

When is the optimal time to secure disability insurance?
There are several reasons for securing disability insurance sooner rather than later. First, insurance companies offer pricing incentives when people lock in policies prior to becoming an attending physician. These discounts stay on for the life of the policy. Second, you have to prove your health to the insurance company only one time, which means that you won't have to answer any additional health questions when you increase your policy amount in the future. Furthermore, if your health changes prior to locking in an initial policy, you may never be able to secure a policy in the future. Last, there are coverage limits that are put into place based on where you are in your career and how much money you are making.

What is the "definition of disability"?
The "definition of disability" is the litmus test that determines whether the insurance company is required to pay out benefits or not. The most comprehensive is "True Own Occupation With Medical Specialty Wording," which provides the best coverage and is ideal for physicians who perform procedures, such as gastroenterologists. However, each company refers to their specific "definition of disability" by a different title, and the best way to differentiate between companies is to compare the specific wording. The difference between "and" or "or" could be the difference of receiving benefits, not receiving benefits, or receiving partial benefits.

Can I modify my disability insurance policy when my earnings increase?
Most individual disability insurance policies have a feature that allows you to increase the policy amount at a later date, and the specific company/policy determines how lenient/rigid the terms are to increase the benefit amount of the policy. Most policies do not ask any medical questions when the policy is increased at a later date, and the increase is calculated based on your health at the policy onset and the age that you are at the time of the increase.

Are all disability insurance policies the same?
Disability insurance is not a standard commodity. No two policies are the same. There are comprehensive policies, mid-range policies, and noncomprehensive policies. The main policy features that differentiate policies are Definition of Disability, Benefit Duration for Mental/Nervous/Substance and Psychiatric Related Claims, Future Increase Option (each company calls this something different), Cost of Living Adjustment (COLA), Residual Rider, Catastrophic Rider, and Student Loan Protection Rider.

How does employer-provided group disability insurance affect individual disability insurance?
Ideally, you should have an individual disability insurance policy prior to becoming an attending physician. When you are an attending physician, strict limits are placed on how much disability insurance you can carry; however, if you lock in a policy prior to becoming an attending then that individual policy will be grandfathered in and will not count toward this limit. On the contrary, if you are an attending physician already, you may be limited in securing an individual disability insurance policy if your employer has already given you a sizeable group disability insurance policy.

What are the differences between group disability coverage and individual disability coverage?
Group disability policies are typically less comprehensive than top-tier individual policies given that many people who are covered by group policies may not otherwise be eligible for individual disability insurance. Second, group policy benefits are typically taxable, while individual policy benefits are typically tax free. Finally, group coverage typically stays behind when you change employers compared to an individual policy that can move with you from job to job.

Does my current income dictate how much disability insurance I can obtain?
As a student, resident, or fellow, your income (or lack thereof) is not a factor when it comes to securing a policy. As an attending physician, your income and the amount of "other" disability insurance (such as group disability insurance) you have dictates how much coverage you are eligible for.

How does relocation affect my disability insurance policy?
When you move, as long as you are current with your premium payments, the policy will not be affected.

Is there increased pricing for policies issued in any locations?
Policies purchased in Florida, California, Arizona, or Nevada have higher rates and verbiage scale backs, which means that the coverage being offered has limitations that are not present in policies issued in other states. If you plan to move to one of these states, I highly recommend that you secure a policy before moving, as you will pay significantly less premium and have more comprehensive coverage.

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How are pre-existing medical conditions factored in?

The impact of a pre-existing medical condition depends on what it is, when it occurred, how it is being treated, and/or what the prognosis is. In some instances, the insurance company excludes claims related to a particular pre-existing condition (you would know this upfront when the policy is secured), while in other instances the insurance company increases pricing or decreases benefit duration. It is also possible that the insurance company does not make any changes to the policy on account of a pre-existing medical condition.

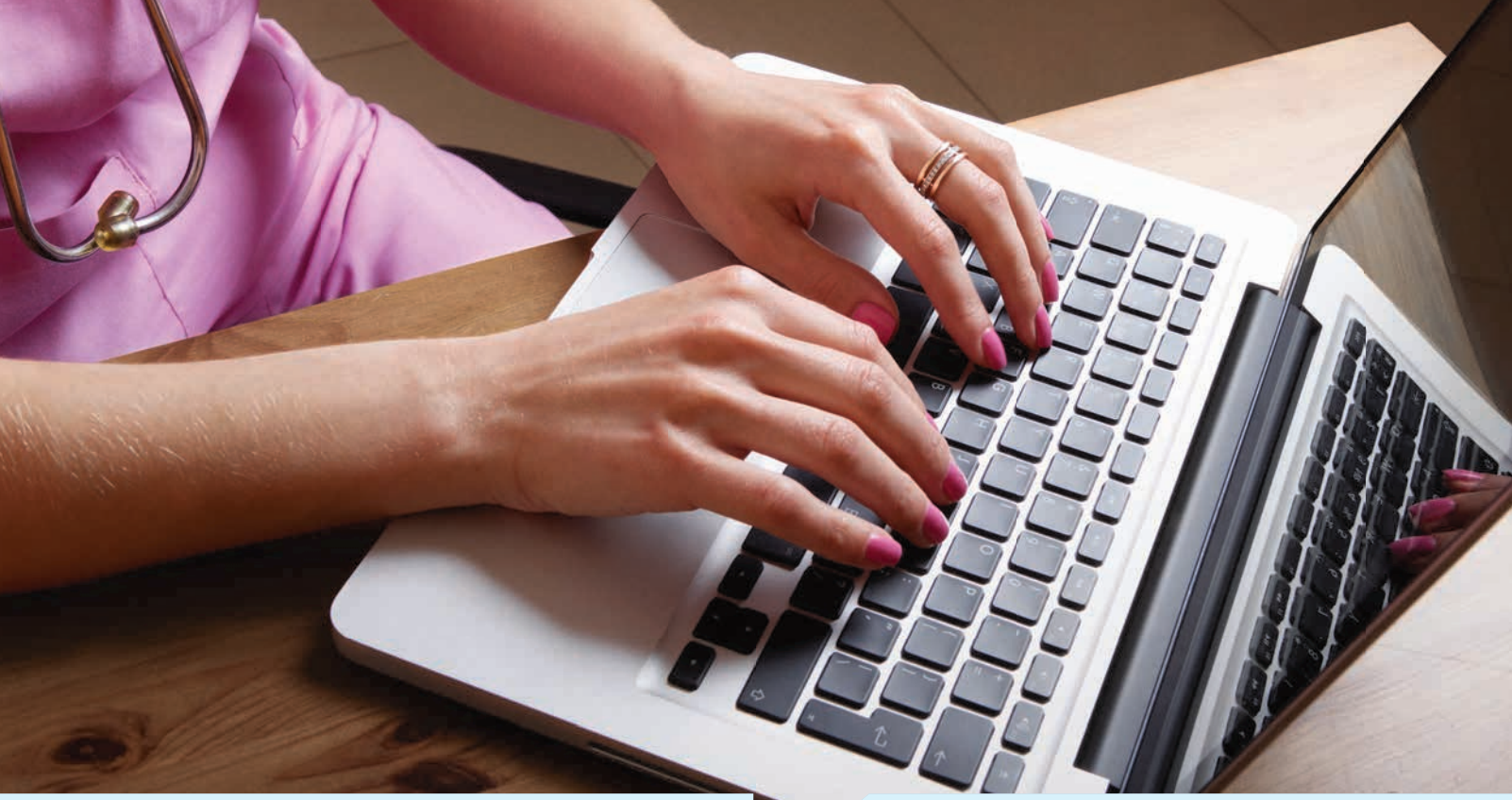
What are the pros/cons of disability insurance policies that do not ask any medical questions or require an insurance exam?

The only time that it makes sense to accept a disability insurance policy that does not ask medical questions and does not require an insurance exam is when you have a serious pre-existing condition that would not allow you to secure a comprehensive policy. These "guaranteed issue" types of policies are scaled back in nature because they are typically obtained by people who are at a higher risk of disability to begin with. If you are in favorable health, it behooves you to pursue a disability insurance policy that requires medical questions/examination.

Does pregnancy affect disability insurance?

Maternity-related claims are one of the fastest rising claims for females. It is possible for females who are pregnant to obtain a disability insurance policy; however, policies that are issued during pregnancy typically have "pregnancy exclusions" on them that may exclude disability that results from the current pregnancy. If a disability insurance policy is in place prior to pregnancy, a pregnancy-related disability should be covered (unless otherwise specified) by this policy. Therefore, it is highly recommended that females secure their disability insurance prior to becoming pregnant.

Individual disability insurance is one of the most important components of a physician's financial plan. There are many types of policies available, but there is only one policy that best suits your goals and objectives. I recommend that you work with an insurance broker that specializes in supporting physicians, because of the nuances within insurance contracts. Should you have any questions, please do not hesitate to contact me at jay@atlanticpension.com. ■



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Sample Size, Patient Selection — Keys to Successful Small Studies

By Whitney McKnight // Frontline Medical News

ORLANDO – Studies with small patient populations but large effect sizes are the backbone of an independent investigator's success. Rigorous patient selection doesn't hurt, either.

"We often hide behind the words 'pilot and feasibility' to justify what was not a very good study," Dr. Joshua Korzenik, director of Harvard Medical School's Crohn's and Colitis Center, Boston, said at a conference on inflammatory bowel diseases sponsored by the Crohn's and Colitis Foundation of America. "The term can indicate something was not statistically significant, and that can be legitimate, but 'pilot' should not be a substitute for not sizing the study appropriately."

Sample size consideration is important with respect to data analysis and endpoints, said Dr. Korzenik, but disciplined selection criteria strictly applied sweeten the odds for a study's impact. Cultivating a cohort that is the "most homogeneous, cleanest, and clearest ... will give you the best insight." Consider choosing patients according to disease subtype, bio- and genetic markers, a history of at least 3 consecutive months of disease, and a history of certain medication failures.

Steer clear of the assumption that just because you already treat a certain number of patients, you will be able to recruit them. "Some patients won't want to commit to a study," warned Dr. Korzenik. "You need to think more carefully."

And don't forget the "tremendous" impact of standard deviation on sample size. Dr. Korzenik recommended the "usual" power of .8 with a *P* value

less than .05 for early phase studies.

For the neophyte independent investigator, sweating over what to write in his or her hypothesis, and struggling against temptation to justify sample size by stretching how small the placebo response will be vs. how great the efficacy rate is only to find actual results are not nearly what was predicted, can be devastating. "Then you've shot yourself in the foot," said Dr. Korzenik.

One problem is that few, if any, previous data exist for these kinds of studies. And preclinical data "tends not to be helpful at all," Dr. Korzenik opined.

"too much." Using a placebo effect size of 10% vs. 50% for the drug, with 17 patients per arm, the investigator runs the risk of overestimating what's possible. "You might need to look for another endpoint, or some other set of collaborators," Dr. Korzenik said.

Open-label studies can be useful for helping with sample size, particularly if the study is to evaluate a novel approach to treatment, but things can still go wobbly. "Open-label trials have limitations we don't fully understand," Dr. Korzenik said.

To wit, open-label trials on the use of the helminth *Trichuris suis* to treat Crohn's disease showed robust response remission rates, but a successive, placebo-controlled trial did not achieve these results. For independent investigators conducting a placebo-controlled trial using a comparator for the control group, Dr. Korzenik suggested ways to keep the placebo response lower. These included, among other strategies, recruiting patients with higher disease activity and keeping trials as short as possible. "When you do longer studies, the placebo response remission rates go up. Keep that in mind."

And, don't forget: Not all small studies with impact need focus on pharmaceuticals. Possibilities Dr. Korzenik suggested include alternative interventions such as marijuana, curcumin, and aloe vera. "These things have been done, but deserve further study," he said, adding that nutritional interventions are "undervalued, and although difficult to study, are very important."

The role of depression, fatigue, and other psychosocial impacts of inflammatory bowel disease are also worthy of study, as are the utility of telemedicine and social media for helping patients, he said.

Because investigators will want to protect their resources – namely, the goodwill of the patients they painstakingly recruited – Dr. Korzenik advised using telemedicine to interact with study participants whenever possible, and to consider using smartphone apps to record symptom data. "Remember that repeated evaluations become an enormous burden on the patient."

Consider choosing patients according to disease subtype, bio- and genetic markers, a history of at least 3 consecutive months of disease, and a history of certain medication failures.

Even in trials for anti–tumor necrosis factor (TNF) drugs, what Dr. Korzenik argued are the most revolutionary treatments to yet impact the field, the question of placebo effect on sample size was tricky. "For the most part, anti-TNFs are about 20% better than placebo for inducing remission. That's a pretty high bar to set, and most investigator-sponsored studies set the bar even higher, making it very difficult."

If, for example, an investigator hopes to achieve a 50% reduction in calprotectin, and so sets a "modest" rate of 20% for placebo and 35% for the test drug, that means the investigator must recruit 136 patients per arm. "Yikes!"

But estimating at 15% vs. 40% for the drug, with 47 in each arm, may push the benefit of the study drug

Dr. Korzenik urged young investigators not to be intimidated, and to see their inexperience as liberation from having preconceived notions of what the correct approaches are to studying IBD. Still, finding a mentor "who can help shape your ideas and help develop techniques," can build confidence.

"You don't necessarily need to have a final piece of work that can stand on its own," Dr. Korzenik concluded. "You're learning how to do a clinical trial and get your career moving forward." ■

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