The NEW GASTROENTEROLOGIST

INSIGHTS FOR FELLOWS & YOUNG GIs A Quarterly Supplement to GI & Hepatology News | Summer 2015

IBD Update

Biologic Therapies for Inflammatory Bowel Disease **12**

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2150-332PUB_15-2

Letter
FROM THE EDITOR

Bryson W. Katona is instructor of medicine in the division of gastroenterology at the University of Pennsylvania.

Dear Colleagues,

With the start of a new academic year, on behalf of the AGA and *The New Gastroenterologist*, I want to congratulate all of the new fellows beginning their GI fellowships, as well as those graduating fellows who are embarking on their first jobs. It is certainly an exciting time of the year!

In this second issue of *The New Gastroenterologist*, we focus on the field of IBD, which continues to advance rapidly with an ever-growing number of therapeutic options. Given the rapid pace of change, it is important to stay on top of the critical studies in the field, as well as the currently approved medications and their dosing schedules for both Crohn's disease and ulcerative colitis. To review the current state of biologic therapy in IBD, Dejan Micic, Andes Yarur, and David Rubin from The University of Chicago have put together a fantastic, concise, and high-yield overview. Furthermore, in a new feature in this issue, former AGA president and current professor at Yale, Loren Laine, gives an insightful interview where he shares some of his experiences as well as advice for achieving a successful career in GI. Also included in this issue of *The New Gastroenterologist* is a perspective on pursuing a transplant hepatology fellowship by Jennifer Lai at the University of California, San Francisco; coverage of Dawn Provenzale's (Duke University) session at DDW® on time management and work-life balance; also from this past DDW®, a fantastic blog of a politically geared session by Gaurav Singhvi from UCLA; as well as a primer on the important aspects of obtaining and maintaining a life insurance policy.

As always, there are many other great resources in this issue of *The New Gastroenterologist* which I encourage you to explore. Additionally, if you would prefer to read *The New Gastroenterologist* "on-the-go," please download our free app from iTunes, Google Play, and Amazon. Finally, as this publication continues to develop, please e-mail me at bryson.katona@uphs.upenn.edu or Erin Dubnansky at edubnansky@gastro.org if you have any comments about this issue or ideas for future issues of *The New Gastroenterologist*.

Sincerely,
Bryson W. Katona, M.D., Ph.D.
Editor-in-Chief

Correction

In Table 3 on page 11 of the Spring 2015 issue, for Genotype 1b, the Treatment Duration for Regimen 1 should be 12 weeks or 8 weeks if RNA < 6 million IU/mL.

The NEW GASTROENTEROLOGIST

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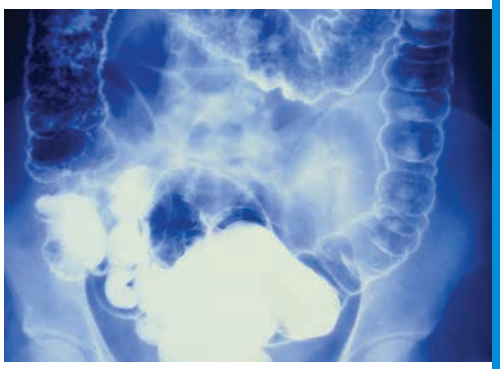
ON THE COVER

Double-contrast barium enema x-ray of the large intestine in ulcerative colitis.

Photo credit: ©SPL / Science Source

IN THIS ISSUE



DDSEP® 7
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QUESTIONS

// Answers on page 22

Q1: A 19-year-old man who underwent a Fontan procedure at 6 years old presents with progressive edema, ascites, chronic diarrhea, and malnutrition. His albumin is 1.7 g/dL and his fecal alpha-1-antitrypsin clearance is 486 mg per 100 mL (normal, < 27 mg per 100 mL), consistent with protein-losing enteropathy. The following therapies have been reported to be helpful in reducing the severity of the condition, except:

A. Heparin
B. Liver transplant
C. Octreotide
D. Medium-chain triglycerides
E. Budesonide

Q2: A 47-year-old man presents to the emergency room with new-onset bloody diarrhea, abdominal pain, and cough. He has a history of plaque psoriasis, and was recently started on etanercept upon returning from military duty overseas. On exam, his temperature is 38.8°C, he has a diffuse petechial rash, and bilateral wheezing. CBC reveals a leukocyte count of 13,000 with a normal differential, chest x-ray shows bilateral infiltrates, and abdominal CT reveals nonspecific thickening of the ascending colon. He is admitted to the hospital, and broad-spectrum antibiotics are initiated.

Which therapy is most likely to be helpful?

A. Albendazole
B. Nitazoxanide
C. Ivermectin
D. Paromomycin
E. Praziquantel

For more information about DDSEP© visit gastro.org/ddsep

What's Your Diagnosis?

An uncommon cause of recurrent duodenal intussusception

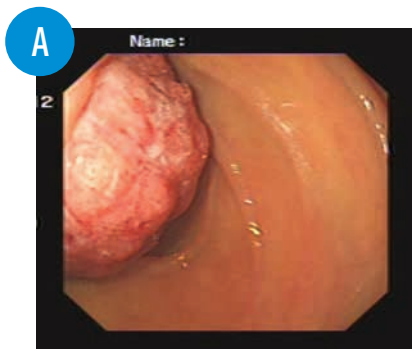
Published previously in Gastroenterology (2014;146:e10-e11)

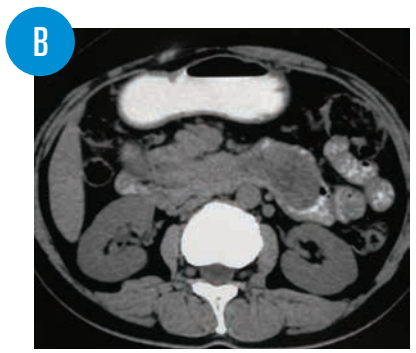
By Huiying Zhao, M.D., Ye Li, M.D., and Dianbo Cao, M.D.

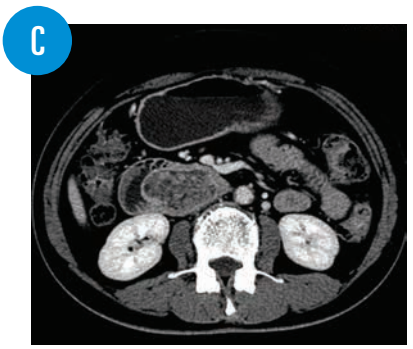
A 49-year-old woman was admitted to our hospital with a 1-year history of intermittent black stool and epigastric pain. She occasionally experienced itchy skin and yellow sclera. Physical examination was unremarkable. Except for the decrease of hemoglobin values down to 76 g/L, all other laboratory values were within the normal limits. Endoscopy before admission showed a long, friable, ulcerated, pedicle-like structure with granular surface on the distal end, extending from the duodenal bulb into the second part of duodenum (Figure A). Axial computed tomography (CT) done 2 months previously showed a proximal jejunal mass and on the next day contrast-enhanced CT showed a mass in the second portion of duodenum, suggesting duodenal intussusception and spontaneous resolution (Figures B, C). Subsequent abdominal CT on admission revealed a duodenal hypodense mass with intussusception involving the duodenum and proximal jejunum (Figure D). No adenopathy, ascites, or other mass lesions were noted. ■

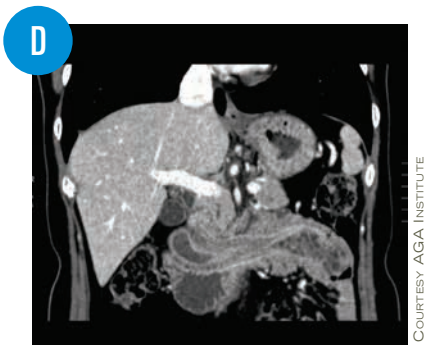
What is the diagnosis?

Dr. Zhao is in the department of internal medicine, and Dr. Li and Dr. Cao are in the department of radiology at the First Hospital of Jilin University, Changchun, China.









COURTESY AGA INSTITUTE

See ***The Answer*** on page 18

News from the AGA

Introducing AGA's New Strategic Plan

AGA has a new Strategic Plan to mobilize the resources of our organization to fulfill our mission of advancing the science and practice of gastroenterology.

"AGA, at our heart, is a learning organization. This new strategic plan will lead us to new discoveries in GI science, new tools to improve patient care, new ways to educate ourselves and the gastroenterologists of the future. Together we will shape a bright future for gastroenterology and our patients," says John I. Allen, M.D., MBA, AGAF, outgoing president, AGA Institute.

In 1897, a group of physicians started the AGA to make a difference in the lives of their colleagues and their patients. Since that time, AGA has been the driving force behind advances that matter in gastroenterology and hepatology research and practice. We have made staggering scientific discoveries and applied them to improve patient care. However, we still have so much more to learn, and that's why the AGA Strategic Plan matters.

Read the plan online at www.gastro.org/about.

Two words describe each of the three fundamental AGA areas as illustrated in the triangular portion of the plan. For example, practice and quality were paired intentionally to emphasize their close connection and the AGA's increasing commitment to increasing the "value" (defined as quality per unit cost) of our GI and liver care. Research is critical to our advancing science, but needs to be coupled with AGA's commitment to promote innovation in medical device and therapeutic advances, through the AGA Center for GI Innovation and Technology and the AGA Center for Diagnostics and Therapeutics. Finally, education must be paired with training our physician and provider workforce in new and emerging technologies. ■

Courtesy AGA Institute

The SGR is Repealed. Now What?

The physician community secured a huge victory in April when Congress finally passed legislation to repeal the broken sustainable growth rate (SGR) formula, which set reimbursement for physicians under Medicare. For years, the entire physician community has been advocating that Congress repeal the broken, outdated formula since it didn't accurately reflect the costs of providing care to Medicare beneficiaries.

Like most major pieces of legislation, the real work will come during implementation. Our work will continue during the regulation and comment period. We know that we have our work cut out for us, but we are confident that AGA has the foundation in place to ensure that our members have the tools they need to survive and thrive in a value-based world. We will continue to work to ensure that the transition to a value-based world is as seamless as possible. ■

AGA Institute co-executive vice president, Lynn P. Robinson, JD, was honored to represent AGA at a historic and awe-inspiring ceremony in the White House Rose Garden to celebrate the signing of the SGR repeal legislation.

New AGA Guideline: Recommendations for Changes in Management of Pancreatic Cysts

A new AGA guideline provides direction to GIs and their patients with incidental pancreatic cysts identified during abdominal imaging. The guideline recommends that most patients with asymptomatic pancreatic cysts should be conservatively monitored with a longer surveillance period and more consideration of risks and benefits before moving to surgery.

To view this guideline, as well as the accompanying technical review and clinical decision tool, visit www.gastro.org/guidelines. ■

Interested in Technology and Innovation?

In March 2015, AGA convened thought leaders for a two-day meeting on the latest innovations and breakthrough technologies in GI.

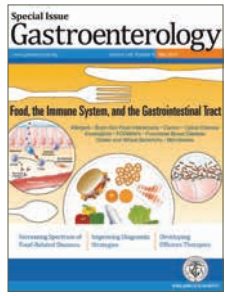
Hot topics at the meeting included:

- An overview of new technologies introduced in the GI medtech market in 2014.
- Insight into how 3-D printing has the potential to change GI care (hint: made-to-order livers).
- Commentary on new obesity treatments, mobile technologies, and behavioral economics.
- Questions to consider when purchasing new technologies.
- AGA's partnership with FDA, focused on bringing new devices to market.

View AGA Tech Summit meeting coverage on GI & Hepatology News (http://www.gihepnews.com/aga-meetings/aga-tech-summit/conference-coverage.html) or watch video interviews from the meeting on AGA's YouTube channel: www.youtube.com/AmerGastroAssn.

Save the date: The 2016 AGA Tech Summit will take place March 31 and April 1, 2016, in Boston. ■

Special Issue of *Gastroenterology* Focuses on Food, the Immune System, and GI Tract



Each May, *Gastroenterology* publishes a special 13th issue that examines a major topic that impacts the science and practice of gastroenterology from a variety of perspectives. This year's issue, "Food, the Immune System, and the Gastrointestinal Tract," reviews the latest research in how food and nutritional elements influence health and disease.

In conjunction with Editor-in-Chief Bishr Omary, Ph.D., M.D., the 13th issue was developed by expert Associate Editors Douglas A. Corley, M.D., Ph.D., and Detlef Schuppan, M.D., Ph.D., from Harvard Medical School in Boston, and the University of Mainz Medical Center in Mainz, Germany. Drs. Corley and Schuppan collaborated with internationally renowned authorities in their respective fields to create a comprehensive issue covering the immunology, biological mechanisms, and latest clinical study findings related to the health effects of food and food-related diseases.

The issue is divided into eight main topics:

- Food and the microbiome
- Food allergies
- Eosinophilic esophagitis
- Food and functional bowel disease
- The clinical spectrum and management of celiac disease
- Nonceliac gluten and wheat sensitivity
- How the brain responds to nutrients
- Nutrients and GI malignancies

The editors hope this special issue will inform future research by identifying gaps in knowledge, while providing both patients and clinicians with evidence-based summaries and clinical recommendations on the interactions of food and the GI tract. Access this special issue by visiting www.gastrojournal.org. ■

AGA Outlook

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

Upcoming AGA Events

Aug. 7-9, 2015
GI Outlook (GO) 2015
"The Practice Management Conference"
Get the tools and knowledge needed to navigate the complexities of today's changing health care environment.
Chicago, IL

Aug. 14-16, 2015
Principles of Gastroenterology for the Nurse Practitioner and Physician Assistant
Hear from the experts as they provide you with information necessary to treat patients in both office and hospital settings. Receive in-depth instruction on many GI topics.
Chicago, IL

Aug. 28, 2015
10th Postgraduate Course on Gastrointestinal Motility and Neurogastroenterology in Clinical Practice
Examine new technologies and medical and nonmedical therapies being utilized to evaluate and treat patients with GI motility and functional GI disorders.
Chicago, IL

Aug. 29-30, 2015
2015 James W. Freston Conference – A Renaissance in the Understanding and Management of IBS
Explore the latest research related to the etiology and pathophysiology of IBS.
Chicago, IL
Funded by the Takeda Endowment

Oct. 1, 2015
Gastroenterology Quarterly Update: October 2015
Listen to an audio conference timed with quarterly release of the CCI edits.
McVey Associates Teleconference –
McVey Associates in collaboration with AGA

Oct. 24-28, 2015
UEG Week 2015
Attend the prestigious GI meeting in Europe for digestive disease professionals.
Barcelona, Spain

Nov. 10, 2015
GI Boards

Awards Application Deadlines

AGA-Takeda Pharmaceuticals International Research Scholar Award in Neurogastroenterology
Deadline: August 14, 2015

AGA-Takeda Pharmaceuticals International Research Scholar Award in Gut Microbiome Research
Deadline: August 14, 2015

AGA-R. Robert and Sally Funderburg Research Award in Gastric Cancer
Deadline: August 21, 2015

Research Scholar Award
Deadline: September 25, 2015

Snapshots from the AGA Journals

Capsule Colonoscopy Has Improved, But Limitations Persist

May Gastroenterology [doi:10.1053/j.gastro.2015.01.025]

Key clinical point: Despite improvements in second-generation capsules, colonoscopy remains the gold standard for colorectal adenoma detection.

Major finding: Compared with conventional colonoscopy, the capsule showed 88% sensitivity and 82% specificity for detecting adenomas of at least 6 mm in subjects who had them.

Data source: Prospective, multicenter, single-blinded comparison of capsule and conventional colonoscopy in 884 asymptomatic subjects.

Disclosures: Given Imaging makes the capsule technology, funded the study, and paid consulting or other fees to Dr. Rex and six coauthors. The other authors reported no relevant conflicts of interest.

Commentary

Dr. Jeffrey Lee, MAS, is assistant clinical professor of medicine in the division of gastroenterology at the University of California, San Francisco. He has no conflicts of interest.

In the United States, colonoscopy is the primary screening test for colorectal cancer. However, because of issues with colonoscopy uptake, costs, and the small but finite risk of complications, the concept of a relatively noninvasive structural examination of the colon that can detect colorectal neoplasia is appealing to both patients and physicians. Although capsule colonoscopy has emerged as a potential noninvasive tool for examining the entire colon, there are limited data on its accuracy for detecting conventional adenomas or sessile serrated polyps, particularly in an average-risk screening population.

In the May issue of Gastroenterology, Dr. Rex and colleagues report their results from a large, multicenter, prospective study evaluating the new second-generation capsule colonoscopy (PillCam COLON 2, Given Imaging) for detecting colorectal neoplasia in an average-risk screening population. Using optical colonoscopy as the reference standard, the capsule colonoscopy performed well for detecting conventional adenomas 6 mm or larger with a sensitivity and specificity of 88% and 82%, respectively. In addition, the sensitivity and specificity of capsule colonoscopy for conventional adenomas 10 mm or larger were 92% and 95%, respectively. However, despite the high performance characteristics for detection of conventional adenomas, the capsule colonoscopy had limited accuracy for detecting sessile serrated polyps 10 mm or larger, with a sensitivity of 33%. Furthermore, nearly 10% of the enrolled subjects were excluded from the analysis because of poor bowel preparation and rapid transit time.

These issues aside, the Rex study provides important information about alternative screening modalities for detection of colorectal neoplasia, particularly for gastroenterologists who may be hesitant or unwilling to perform an optical colonoscopy in high-risk patients with significant comorbidities or in patients who had an incomplete colonoscopy. ■

Two-Way Link Found Between IBD and Cervical Cancer

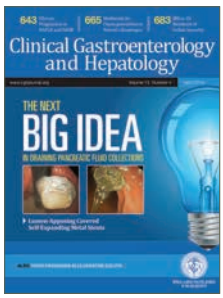
April Clinical Gastroenterology and Hepatology [doi:10.1016/j.cgh.2014.07.036]

Key clinical point: Inflammatory bowel disease – particularly Crohn's disease – might increase risk of cervical cancer.

Major finding: Women with Crohn's disease had an estimated 53% increase in risk of developing cervical cancer, compared with controls.

Data source: Population-based cohort study of 27,408 women with inflammatory bowel disease and 1,508,334 controls.

Disclosures: The study was funded in part by the Danish Council of Independent Research. The investigators reported having no relevant financial disclosures.



Commentary

Dr. Edward V. Loftus Jr., AGAF, is professor of medicine and director of the inflammatory bowel disease interest group, division of gastroenterology and hepatology, at the Mayo Clinic, Rochester, Minn. He has consulted for and received research support from UCB, AbbVie, and Janssen.

The possibility that intraepithelial neoplasia or dysplasia of the uterine cervix might occur more frequently in women with inflammatory bowel disease (IBD) was raised almost 10 years ago. It stands to reason that some women with Crohn's disease or ulcerative colitis might be at increased risk of cervical dysplasia – after all, the primary driver of cervical neoplasia is infection with human papillomavirus, many patients with IBD are on drugs that suppress the immune system, and other immunosuppressive states (for example, HIV infection, post organ transplant) have been associated with higher rates of cervical dysplasia and cancer. However, the results of studies on this question have been conflicting.

These researchers from the Statens Serum Institut in Copenhagen have harnessed the power of the nationwide Danish medical informatics system to answer many epidemiologic questions about various aspects of IBD. The researchers identified a cohort of more than 18,000 women with ulcerative colitis, more than 8,000 women with Crohn's, and more than 1.5 million women with neither, and "followed" them through a pathology registry for cervical dysplasia and through a cancer registry for cervical cancer. Access to a prescription registry allowed stratification of risk based on medication use. Careful review of the methods section of the paper suggests that this study was well designed and executed.

Women with ulcerative colitis were about 15% more likely than controls to develop dysplasia, but the cancer risk was not increased. Women with Crohn's disease were about 25% more likely to develop dysplasia relative to controls and more than 50% more likely to develop cervical cancer. There were no significant differences in neoplasia risk when stratified by medication use, although there were trends toward increased risk of high-grade cervical dysplasia in women with Crohn's disease who were prescribed azathioprine or anti–tumor necrosis factor agents. Interestingly, the risk of cervical neoplasia was elevated in women well before the diagnosis of IBD.

The study confirms that there is an elevated risk of cervical dysplasia and cancer among women with IBD, and that the risk seems slightly higher in those with Crohn's disease. The finding of the increased risk of neoplasia well before the diagnosis of IBD suggests that perhaps a relative state of immunosuppression exists in patients who are ultimately diagnosed with IBD. In some respects, I found this to be the most intriguing aspect of the paper, and it needs to be explored further in both prospective and retrospective studies. ■

Oxidized Low-Density Lipoprotein Predicted Chronic HCV Interferon Response

May Cellular and Molecular Gastroenterology and Hepatology [doi:10.1016/j.jcmgh.2015.03.002]

Key clinical point: Oxidized low-density lipoprotein prevented hepatitis C virus from entering hepatocytes and predicted interferon-based treatment response among patients with chronic HCV infection.

Major finding: Serum oxLDL levels independently predicted SVR after treatment with pegylated interferon/ribavirin ($P < .001$).

Data source: In vivo study of 379 patients with chronic genotype 1 HCV infection, and in vitro study of HCV replication in hepatoma cells.

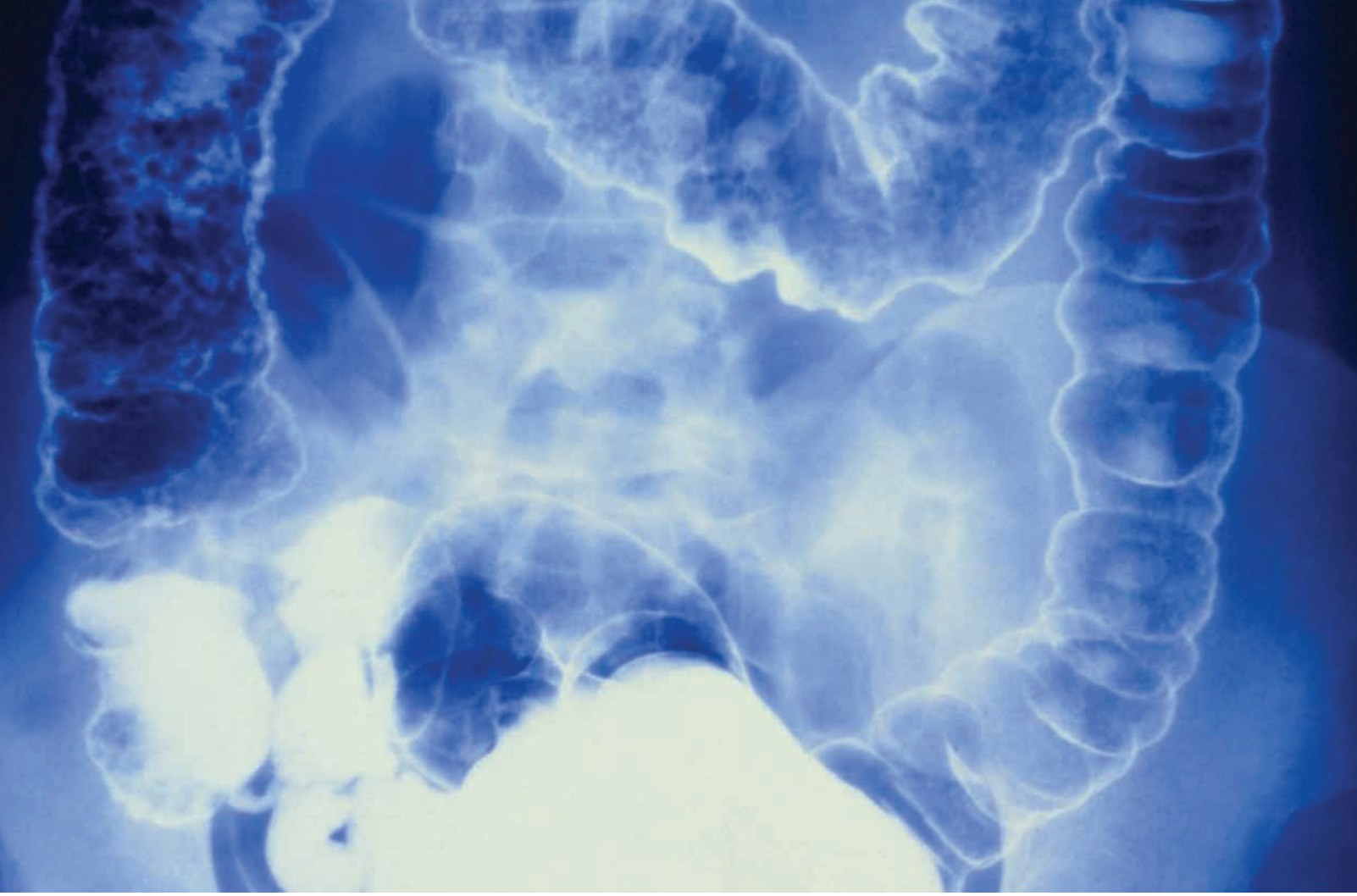
Disclosures: The Germany Center for Infection Research partially funded the study. Five coauthors reported having served as clinical researchers, consultants, or speakers for MSD/Merck and Roche. The other authors reported no relevant conflicts of interest.

Commentary

Dr. Markus von Schaewen and Dr. Alexander Ploss are in the department of molecular biology, Princeton University, N.J. They have no conflicts of interest.

Despite the fact that significant advances in the treatment of hepatitis C have been made, it is still a major global health burden. In order to follow up on their previous observation that oxLDL acts as a hepatitis C virus (HCV) entry inhibitor by disrupting the interaction between HCV and one of its entry factors, scavenger receptor type B class I (SR-BI), Dr. Solbach and his associates analyzed the oxLDL levels of 379 patients from the INDIV-2 study chronically infected with HCV genotype 1. The authors demonstrated that baseline oxLDL serum levels were an independent predictor of a sustained virologic response in interferon-based treatment regimens and that LDL is a sufficient surrogate marker.

Clinicians, especially in resource-limited environments, may take oxLDL or LDL serum levels into consideration for treatment decisions, although these predictors are unlikely to broadly affect treatment decisions in real-world settings. The significance of this study lies more in adding to our understanding of the pathophysiology of HCV. The data presented here indicate that the observed effect of oxLDL is possibly due to an oxLDL-mediated inhibition of HCV cell-to-cell spread. Taken together with their previous observation that oxLDL interferes with the interaction of HCV and its entry factor SR-BI, the authors provide additional evidence that SR-BI may be needed for cell-to-cell spread of HCV and might thereby have implications for the further development of HCV entry inhibitors. ■



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Biologic Therapies for Inflammatory Bowel Disease

By Dejan Micic, M.D., Andres J. Yarur, M.D., and David T. Rubin, M.D.

Dr. Micic, Dr. Yarur, and Dr. Rubin are at The University of Chicago Medicine Inflammatory Bowel Disease Center. Dr. Rubin has received consultant and grant support from AbbVie, Janssen, UCB, Takeda, Amgen, Pfizer, Genentech, and Prometheus Labs.

The inflammatory bowel diseases (IBD) can be classified into two main entities, Crohn's disease (CD) and ulcerative colitis (UC). They are generally characterized by a relapsing-remitting course requiring frequent use of immunosuppressant medications and surgical interventions for complicated or intractable disease (1). In UC, acute and chronic inflammation confined exclusively to the mucosa of the colorectum is the hallmark of the disease. In CD, the clinical course may include the development of stricturing disease, fistulous tracks, and intra-abdominal infections. Although the pathogenesis of IBD is not well understood, the current premise is that defects in the immune system allow for aberrant immune responses to intraluminal antigens, which ultimately lead to bowel damage (2).

Historically, a step-up approach to medical care has included the use of aminosalicylate derivatives, corticosteroids, methotrexate, thiopurines, and biologic agents with separate goals of an induction of clinical remission and maintenance of disease control. Some of the conventional nonbiologic therapies have resulted in symptomatic improvements, but have failed to improve long-term outcomes or induce mucosal healing (3). Therefore, current treatment algorithms and proposed goals of treatment include the earlier use of biologic therapies with a new focus on objective treatment responses (4). Particularly among patients with a high risk of disease progression (disease phenotype, young age at diagnosis, severe endoscopic lesions, disease requiring surgical therapy), biologic therapy is advocated early in the disease course in order to alter the natural history of the disease process.

Anti-TNF biologic therapies for CD

The advent of biologic therapies has revolutionized treatment strategies and endpoints with demonstrated effectiveness in the induction and maintenance of clinical and endoscopic disease activity. Currently, three anti–tumor necrosis factor (TNF) agents have been approved by the FDA for the treatment of CD: infliximab, adalimumab, and certolizumab pegol. Infliximab is a chimeric monoclonal IgG1 antibody that was the first biologic therapy approved for use by the FDA for IBD in 1998. The ACCENT I and ACCENT II trials initially demonstrated that scheduled maintenance therapy with infliximab is superior to episodic therapy to maintain response and remission in both luminal and fistulizing CD (2, 5, 6). In the ACCENT I trial, 573 patients with active CD were randomized to infliximab-loading infusions and then every 8 weeks in comparison to placebo with a co-primary endpoint of response at week 2 and clinical remission at week 30. At week 30, 39% of patients receiving 5 mg/kg infliximab and 45% of patients receiving 10 mg/kg infliximab were in clinical remission compared to 21% receiving placebo (P = .003 and P = .0002, respectively) (5). Similarly, the ACCENT II trial extended the results of maintenance therapy to fistulizing CD, demonstrating that 36% of patients receiving maintenance infusions of infliximab had the absence of draining fistulas at week 54 compared to 19% of patients receiving placebo (P = 0.009) (6).

Adalimumab is a fully human recombinant IgG1 monoclonal antibody also approved for the treatment of CD (2). In the CLASSIC I trial, 299 patients with moderate to severe CD were randomized to subcutaneous adalimumab at weeks 0 and 2 with a primary endpoint of clinical remission at week 4. The rate of clinical remission was 36% in those receiving adalimumab compared to 12% in the placebo group (P = .001) (7). The CLASSIC II study demonstrated the effectiveness of adalimumab as a maintenance therapy as patients who received weekly or every-other-week adalimumab had higher rates of remission at week 56 (83% and 79%, respectively) compared to 44% for placebo (P < .05 for both comparisons) (8).

Certolizumab pegol is a pegylated humanized antigen binding fragment (Fab) that binds TNF and is also administered subcutaneously (2). The phase III studies evaluating certolizumab pegol use for induction and maintenance in moderate to severe CD included PRECISE-I and PRECISE-II. In PRECISE-I, 662 adults were randomized to certolizumab pegol or placebo with a primary endpoint of induction of a response. At week 6, the response rate was 35% in those receiving certolizumab pegol and 27% in the placebo group, although rates of clinical remission did not differ significantly (P = .17) (9). Among those with a clinical response at week 6, the PRECISE-II study evaluated the efficacy of certolizumab pegol administered every 4 weeks as a maintenance therapy. At week 26, 63% of those receiving certolizumab pegol maintained clinical response as compared to 34% of those receiving placebo (P < .001) (10).

Currently, three anti-TNF agents have been approved by the FDA for the treatment of CD.

Given the success rates achieved with biologic therapies, but the rela-

tively high rate of loss of response, a primary aim is to optimize long-lasting effectiveness (11, 12). The demonstration of a decreased rate of immunogenicity to biologic therapies when used in combination with immunomodulators led to the use of early combined immunosuppression. The landmark SONIC trial randomized 508 patients with moderate to severe CD to infliximab monotherapy, azathioprine monotherapy or combined immunosuppression. With a primary outcome of corticosteroid-free remission at 26 weeks, the endpoint was met in 56.8% randomized to combination therapy, 44.4% receiving infliximab alone, and 30% receiving azathioprine alone ($P < .001$ for comparison with combination therapy and $P = .006$ for comparison with infliximab). Furthermore, mucosal healing occurred at week 26 in 43.9% in the combination therapy group, 30.1% in the infliximab monotherapy arm, and 16.5% receiving azathioprine (13).

The landmark SONIC trial randomized 508 patients with moderate to severe CD to infliximab monotherapy, azathioprine monotherapy or combined immunosuppression.

Anti-TNF biologic therapies for UC

There are three anti-TNF agents approved for the treatment of moderately to severely active UC: infliximab, adalimumab, and golimumab. In the initial studies looking at the efficacy of infliximab for induction and maintenance of remission in UC (ACT-1 and ACT-2), patients with UC were randomized to infliximab loading and 8-week maintenance therapy compared to placebo for 46 weeks (ACT-1) or 22 weeks (ACT-2). Clinical response at week 8 was higher in those receiving 5 mg/kg infliximab (69%) and 10 mg/kg infliximab (61%) compared to 37% of patients receiving placebo ($P < .001$ for both comparisons). In the ACT-2 trial, 64%-69% of patients receiving infliximab achieved clinical response at week 8 compared to 29% receiving placebo ($P < .001$ for both comparisons) (14).

Adalimumab was also evaluated for moderately to severely active UC in 494 patients in a phase III 52-week placebo-controlled trial (ULTRA 1 and 2). Adalimumab loading doses were administered and therapy was continued every other week beginning at week 4. Rates of clinical remission at week 8 were 16.5% on adalimumab therapy and 9.3% on placebo ($P = .019$). When assessing patients not previously exposed to anti-TNF therapy, remission rates at week 8 were 21.3% on adalimumab and 11% on placebo ($P = .017$) (15).

The most recently approved anti-TNF agent in the United States for moderate to severe UC is golimumab. The phase III (PURSUIT-SC) study included 1,064 patients and compared varying induction doses to placebo. Clinical response at week 6 was achieved by 51% in the group randomized to 200 mg/100 mg and 54.9% of patients randomized to the 400 mg/200 mg dose, compared with only 30.3% in the group randomized to placebo ($P < .0001$ for both comparisons) (16). In the follow-up PURSUIT-M study, patients that initially achieved response to induction therapy were randomized to 50 mg or 100 mg golimumab every 4 weeks or placebo through week 52. Clinical response was maintained through week 52 in 47%-49.7% of those receiving golimumab compared to 31.2% among those receiving placebo ($P < 0.01$ for both comparisons) (17).

Table 1

FDA APPROVED BIOLOGIC THERAPIES FOR IBD

Medication	Approved Condition	Route of Administration	Dose	Loading (w)	Maintenance (w)
Infliximab	CD/UC	IV	5 mg/kg	0,2,6	every 8
Adalimumab	CD/UC	SQ	40 mg	0*,2*	every 2
Certolizumab pegol	CD	SQ	400 mg	0,2,4	every 4
Golimumab	UC	SQ	100 mg	0*,2	every 4
Natalizumab	CD	IV	300 mg	0	every 4
Vedolizumab	CD/UC	IV	300 mg	0,2,6	every 8

CD: Crohn's disease; IV: intravenous; SQ: subcutaneous; UC: Ulcerative colitis; w: week
*Loading requires dose increase

Dr. David T. Rubin

Courtesy University of Chicago

Similar to CD, combination therapy with infliximab and azathioprine was compared to monotherapy with either agent in a 16-week randomized controlled trial (UC SUCCESS). The primary endpoint of the study was corticosteroid-free remission at weeks 8 and 16. Corticosteroid-free remission at week 16 was achieved by 39.7% of patients receiving combination therapy, compared to 22.1% receiving monotherapy with infliximab and 23.7% receiving azathioprine alone ($P = .017$ and $P = .032$, respectively). Mucosal healing at week 16 was statistically significantly higher in those receiving combination therapy (62.8%) compared to monotherapy with azathioprine (36.8%) and numerically higher compared to those receiving monotherapy with infliximab (54.6%) (18).

Anti-integrin biologic therapy for CD and UC

While most of the approved biologic therapies for IBD target TNF, another class of available agents target leukocyte trafficking from the endothelium to the bowel. The first anti-integrin therapy approved for CD was natalizumab, a humanized IgG4 monoclonal antibody to alpha4 integrin that blocks the adhesion and subsequent leukocyte migration across the endothelium (2). The efficacy of natalizumab as an induction and maintenance therapy for CD was published together in two phase III clinical trials, ENACT-1 and ENACT-2. In ENACT-1, 905 patients were randomized to receive natalizumab or placebo. At 10 weeks, natalizumab and placebo had similar rates of response (56% and 49%, respectively) and clinical remission (37% and 30%, respectively) ($P = .05$ and $P = .12$, respectively) (19). When continued in ENACT-2, 339 patients that had a response to natalizumab in the first trial were reassigned to natalizumab or placebo with a primary outcome of a sustained response through week 36. Continuing natalizumab led to a higher rate of sustained response compared to placebo (61% vs. 28%) ($P < .001$) (19). A subgroup analysis of patients with an elevated C-reactive protein demonstrated 10-week clinical response in 58% of the natalizumab-treated patients and 48% of the patients in the placebo arm in ENACT-1 (19). This finding led to the publication of the ENCORE trial randomizing patients with moderately to severely active CD and an elevated C-reactive protein to natalizumab or placebo. An induction of response occurred in 48% of the natalizumab treated patients and 32% of the placebo treated patients ($P < .001$), ultimately leading to the approval of natalizumab (20).

Given the highlighted risk of progressive multifocal leukoencephalopathy (PML) with natalizumab, the development of gut selective therapy for both CD and UC has led to the development of vedolizumab, a humanized monoclonal antibody against the alpha4-beta7 integrin. The phase III trial (GEMINI II) included patients with active CD. At a 52-week endpoint, among those patients who achieved a clinical

response 6 weeks after the initiation of therapy, 39% randomized to vedolizumab compared to 21.6% randomized to placebo were in clinical remission ($P < .001$). Furthermore, glucocorticoid-free remission and the number of patients achieving a greater than 100-point decrease in the Crohn's disease activity index (CDAI) were statistically significantly higher in those randomized to vedolizumab (21).

Similarly for UC, the GEMINI I trial demonstrated the efficacy of vedolizumab as an induction and maintenance therapy. Among participants included in the study, 41% had previous failure to more than one anti-TNF agent. Following 6 weeks of treatment, 47.1% of patients receiving vedolizumab demonstrated a clinical response compared to 25.5% of patients receiving placebo ($P < .001$). In addition, 40.9% of patients achieved mucosal healing compared to 24.8% with placebo, a treatment goal associated with improved long-term outcomes (22-24).

Table 2 BIOLOGIC IBD DRUG THERAPIES

			Trial Name	Year	Reference Number
Anti-TNF Therapies					
	CD				
		Infliximab	ACCENT I	2002	5
			ACCENT II	2004	6
		Infliximab + AZA	SONIC	2010	13
		Adalimumab	CLASSIC I	2006	7
			CLASSIC II	2007	8
		Certolizumab	PRECISE-I	2007	9
			PRECISE-II	2007	10
	UC				
		Infliximab	ACT-1/ACT-2	2005	14
		Infliximab + AZA	UC SUCCESS	2014	18
		Adalimumab	ULTRA 1/2	2012	15
		Golimumab	PURSUIT-SC	2014	16
			PURSUIT-M	2014	17
Anti-integrin Therapies					
	CD				
		Natalizumab	ENACT-1/2	2005	19
			ENCORE	2007	20
		Vedolizumab	GEMINI II	2013	21
	UC				
		Vedolizumab	GEMINI I	2013	24

CD: Crohn's disease; IV: intravenous; SQ: subcutaneous; UC: Ulcerative colitis; w: week

Advances in biologic therapy

The increased use of biologic therapies has led to evidence with respect to the optimal use and monitoring of drug therapy (25). Factors associated with improved treatment responses have included early initiation of biologic therapy, maintenance dosing schedules, and the use of concomitant immunosuppression (13, 26-28). In addition, the ability to monitor drug levels (clinically available for infliximab and adalimumab) and metabolites has led to multiple studies looking into the association between drug levels and medication efficacy (29-31). Future studies will continue to look into therapy optimization algorithms in addition to the incorporation of objective disease monitoring techniques to assess response and modifications of therapy (19, 21, 32-38).

Research opportunities

Despite the widespread availability of biologic therapies, it is estimated that < 15% of patients with IBD currently receive anti-TNF therapy (39). The field of biologic therapies and novel therapeutic algorithms is an exciting field for young-career gastroenterologists that allows for the development of niche clinical research programs. The appropriate selection of patients depends on the clinical characteristics of the patient, previous response to medical therapies, and comorbid conditions. Continued demonstrations of changes to the natural history of IBD will require assessment of the long-

term benefits of therapeutic choices while balancing the side effects of therapy (40). Future studies are required to guide the optimization of drug therapies in order to maximize long-lasting objective outcomes. ■

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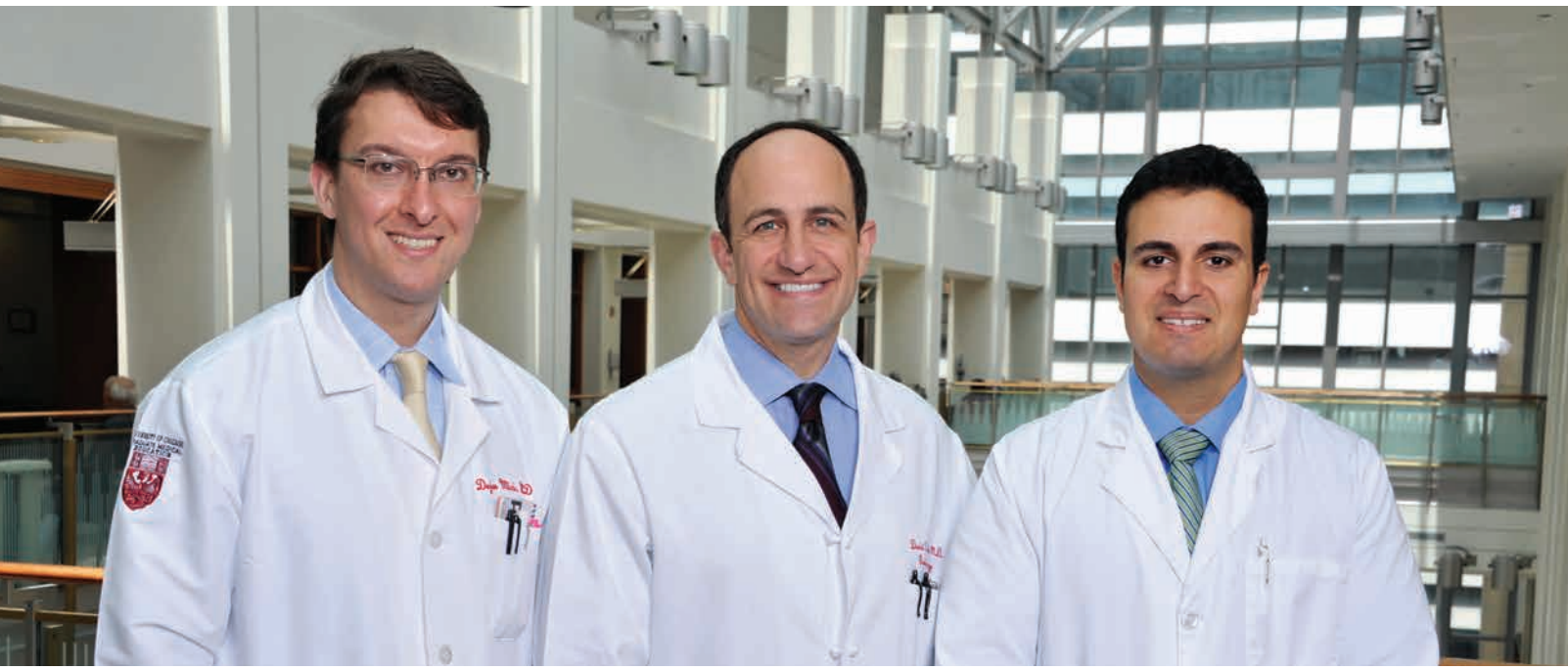
Courtesy University of Chicago



Dr. Dejan Micic, Dr. David T. Rubin, and Dr. Andres J. Yarur of The University of Chicago Medicine Inflammatory Bowel Disease Center.

The Answer

From ***What's Your Diagnosis?*** on page 5

Intraoperatively, duodenal intussusception was found associated with the leading edge of a firm mass in the proximal jejunum. Manipulation of the mass back to the duodenum was successful and the mass was removed by local excision of the tumor pedicle (Figure E). On its cut surface, it resembled a pancreas or salivary gland with multiple cystic spaces (Figure F). Histopathologically, the mass was a typical Brunner's gland hamartoma (Figure G). Brunner's gland adenoma (BGA), also known as Brunneroma or polypoid hamartoma, is a rare, benign, proliferative lesion arising from Brunner's gland of the duodenum, accounting for 10.6% of benign tumors of the duodenum. Development of BGA may be related to chronic renal failure, chronic pancreatitis, and peptic ulcer disease, or *Helicobacter pylori* infection.[1] These lesions are most commonly located in the duodenal bulb and less frequently the second and the third portions of duodenum. Most are asymptomatic and discovered incidentally. In symptomatic patients, the most common manifestations are gastrointestinal hemorrhage and duodenal obstruction. Obstructive symptoms depend on the tumor's size and location. There also have been reports of these hamartomas presenting as painless jaundice, chronic pancreatitis, chronic diarrhea, acute pancreatitis, and biliary fistula.[1] BGA may also present with gastric outlet obstruction, duodenal obstruction, or occasionally with intussusception of the duodenal wall.

Our patients' occasional yellow skin and sclera discoloration suggests intermittent biliary obstruction owing to the intussusception. Duodenoduodenal or duodenojejunal intussusception is very rare in adults because the duodenum is fixed in the retroperitoneum.[2] The diagnosis of intussusception can easily be established, but to make a diagnosis for BGAs can be difficult because they are usually covered by normal mucosa, making pinch biopsy obtained during endoscopy nondiagnostic. CT is regarded as the modality of choice for its evaluation, including its origin, internal composition, enhancement pattern, and extent of the lesion. When BGA is small or pedunculated, endoscopic polypectomy is satisfactory. Open operative excision is reserved for cases where snaring has failed or the tumor is too large. ■

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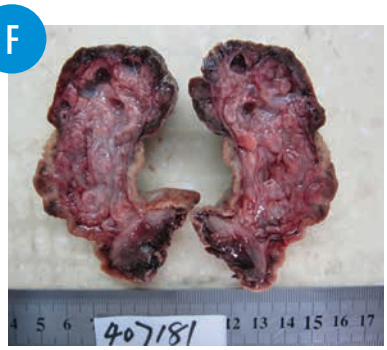
E

F



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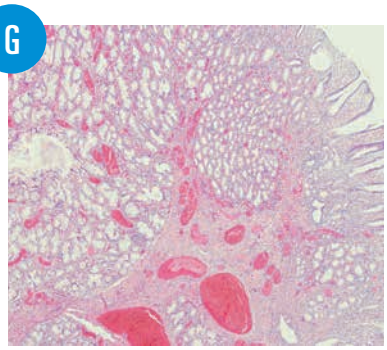

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Physicians Should be Involved in the Political Process

By Gaurav Singhvi, M.D., AGA PAC Board of Advisors

Dr. Singhvi is clinical assistant professor of medicine, David Geffen School of Medicine at the University of California, Los Angeles, and a member of the AGA PAC Board of Advisors.

I just returned from attending DDW® in our nation's capital. As usual, it was a great meeting – I learned about new cutting-edge procedures and exciting therapies for challenging diseases, caught up with old friends, and networked with colleagues.

The highlight of the meeting, without a doubt, however, was the session sponsored by the AGA Government Affairs Committee titled "Why Should Physicians Be Involved in the Political Process? An Insider's View." The session was chaired by Dr. Peter Margolis, who also chairs the committee. Washington, D.C., was the perfect venue for this topic, which has an disproportionate influence on our profession, practice, and patients.

The first talk, "Moving Beyond the Medicare SGR Payment Formula," was given by Bob Jasak from Hart Health Strategies. The repeal of the SGR [Sustainable Growth Rate formula] and replacement with MACRA (Medicare Access and CHIP Reauthorization Act) in April was a great achievement and something that AGA had been working on tirelessly for many years.

The next step, moving to a value-based reimbursement, is a complex process, all the details of which are still in the process of being worked out. Mr. Jasak gave a comprehensive overview of the legislation. An attorney with several years of experience in the health care policy arena, he provided valuable insight on what he thinks the law will mean for GI practices. The main takeaways were the consolidation of quality programs and how compliance with these and other quality measures will dramatically impact reimbursement in the coming years.

The Honorable Phil Roe, a Republican representing Tennessee's 1st House District, was the next speaker. As a retired OB-GYN, Dr. Roe brings a physician's perspective to Congress. Dr. Roe was extremely engaging, knowledgeable, and forthright. He described his path through politics to the U.S. House of Representatives from private practice.

Dr. Roe's goals during this Congress include repealing the Independent Payment Advisory Board (IPAB) and making the implementation of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) a smooth process. He believes both can be achieved in a bipartisan fashion. The IPAB is an unelected body with a broad mandate to achieve savings in the Medicare program. Dr. Roe discussed NIH funding, veterans health care, and graduate medical education funding in an open and frank question-and-answer session.

He also expressed his strong support for colorectal cancer screening and removing any barriers to colonoscopy (such as passing the Supporting Colorectal Examination and Education Now or SCREEN Act) in very personal terms; his wife unexpectedly and tragically died of colon cancer earlier this year.

I came away from the session energized and inspired. This was the first DDW®, as far as I am aware, that was addressed by a sitting member of Congress. As important as the scientific breakthroughs described at DDW® are, the only way they can be realized is if physicians take the initiative and get involved with the policy side of medicine.

There are numerous critical issues facing the GI community, as discussed above. We need to ensure that we have a seat at the table so we can fight for our profession and patients. This can be as simple as reaching out to one's representative in the House or state legislatures. We play a critical role in the lives of their constituents (our patients) and they will respond to these powerful stories.

I encourage all AGA members to get involved in this process. ■

[Dr. Roe] also expressed his strong support for colorectal cancer screening and removing any barriers to colonoscopy (such as passing the Supporting Colorectal Examination and Education Now or SCREEN Act) in very personal terms; his wife unexpectedly and tragically died of colon cancer earlier this year.

DDSEP® 7
Digestive Diseases Self-Education Program®

ANSWERS

// From page 4

Q1: ANSWER: B

CRITIQUE

Protein-losing enteropathy (PLE) is a common complication of the adult survivors of a childhood Fontan procedure. This cardiac surgery can lead to secondary lymphangiectasia of the intestine, probably a consequence of right-sided heart failure with pulmonary hypertension. Intestinal lymphangiectasia leads to the loss of lymph intraluminally, with subsequent protein and lipid malabsorption. PLE is characterized by hypoalbuminemia, hypogamma globulinemia, and diffuse hypoproteinemia, all of which contribute to reduced oncotic pressure with resultant ascites and peripheral edema. Luminal protein loss can be measured by checking the fecal alpha-1-antitrypsin clearance.

Supportive treatment of PLE involves maintaining adequate nutrition with a high-protein diet, and avoidance of excessive stimulation of intestinal lymph flow by maintaining a restriction in long-chain fatty acids. Supplementation with medium-chain triglycerides is often required to provide lipid calories, as these are preferentially absorbed through the venules and not the lacteals. However, MCT oil supplements cannot provide essentially fatty acids. Ultimately, cardiac transplantation should be considered to address this issue. Liver transplant would play no role in reducing lymphatic leakage into the intestinal lumen.

Several medical therapies have been reported to be helpful in reducing diarrhea, malabsorption, ascites, or protein losses associated with PLE. These include heparin, budesonide, octreotide, and sildenafil. The use of heparin sulfate is of great interest in the post-Fontan population in particular. Transmembrane proteins called syndecans maintain tight junctions between epithelial cells. Heparin is an analog and in animal studies with syndecan-deficient mice, heparin corrects paracellular protein losses into the lumen. Both inflammatory cytokines and raised venous pressure exacerbate protein loss in these animal models, which lend biologic plausibility to the reported observations of clinical benefit to both budesonide and octreotide. Sildenafil is often used in this population to reduce pulmonary hypertension and may reduce lymphatic leakage as a consequence.

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Q2: ANSWER: C

CRITIQUE

This patient has hyperinfection syndrome with Strongyloides, which was triggered by the initiation of his anti–tumor necrosis factor agent. This condition has a high fatality rate. Patients may have a polymicrobial bloodstream infection, so broad-spectrum antibiotics should be initiated in all. Stopping the immunosuppressive therapy should be considered, and therapy with ivermectin should be initiated. Although albendazole can be used in Strongyloides infection, studies have not shown it to be as effective as ivermectin. Although combination therapy with both ivermectin and albendazole has been reported in hyperinfection syndrome, ivermectin is the superior monotherapy. The other agents listed, namely nitazoxanide, paromomycin, and praziquantel, are not used in Strongyloides treatment.

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A Medical Career: How to Achieve it AND Keep Your Balance

By Neil Osterweil // At DDW® 2015, Washington

Don't let anyone tell you otherwise: you CAN have it all. You just can't have it all at once.

Whatever circus metaphor you prefer – balancing act, juggling, tightrope walking – achieving and maintaining a satisfactory work/life balance is no mean feat.

"At this point in my career I would like to say that I have this figured out, but I don't. It's a constant balance, and a constant challenge to identify priorities and better understand where you're needed at each particular point in your career and your family situation," said Dr. Dawn Provenzale, a professor of medicine at Duke University Medical Center in Durham, N.C.

She provided tips at the annual Digestive Disease Week for how to balance personal, patient, family, and departmental demands with your career goals.

When time is out of joint

Effective time management is essential to achieving, if not work/life nirvana, at least a sense of order out of chaos.

You may have a time management problem if you feel that your life is out

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of control, you frequently miss deadlines, are unable to say "No" to myriad demands, are easily interrupted or distracted, or spend too much time reacting to crises rather than proactively addressing potential problems areas of your life, Dr. Provenzale said.

She recommended starting to get control by keeping a log of how you spend your time, using one of many different tools freely available on the Internet or as smartphone apps.

Dr. Provenzale believes that once you have a better handle on how your time is spent, you can begin planning for what bestselling author and time-management guru Dr. Stephen R. Covey ("The 7 Habits of Highly Effective People") calls "Wildly Important Goals."

"So, what are your goals? What's your big picture? Do you want an academic career? Are you seeking promotion over time? Are you trying to build a private practice? It's taking a step back and thinking what do you want, and how you might get there that [should be the next step]."

Build an infrastructure

The cornerstone of your work/life balance plan should be a mentor, whether she or he is a colleague in your division or at another practice in your community, or a member of state or national societies in your profession.

"This mentor will help identify your strengths in spite of challenges, will be there to give you a word of encouragement, even when things are not going in a good direction,

The cornerstone of your work/life balance plan should be a mentor, whether she or he is a colleague in your division or at another practice in your community, or a member of state or national societies in your profession.

will guide you professionally and help you see the big picture – your goal or promotion – and what steps are needed to get to that point," Dr. Provenzale said.

It's also important to seek support from others, such as peers who might be able to take one of your shifts when you have a family commitment, a neighbor who can drive your kid to school when you have an early meeting, hired staff (if you can afford them) such as nannies and housekeepers, and mostly importantly, from your partner or spouse.

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Keep the balance

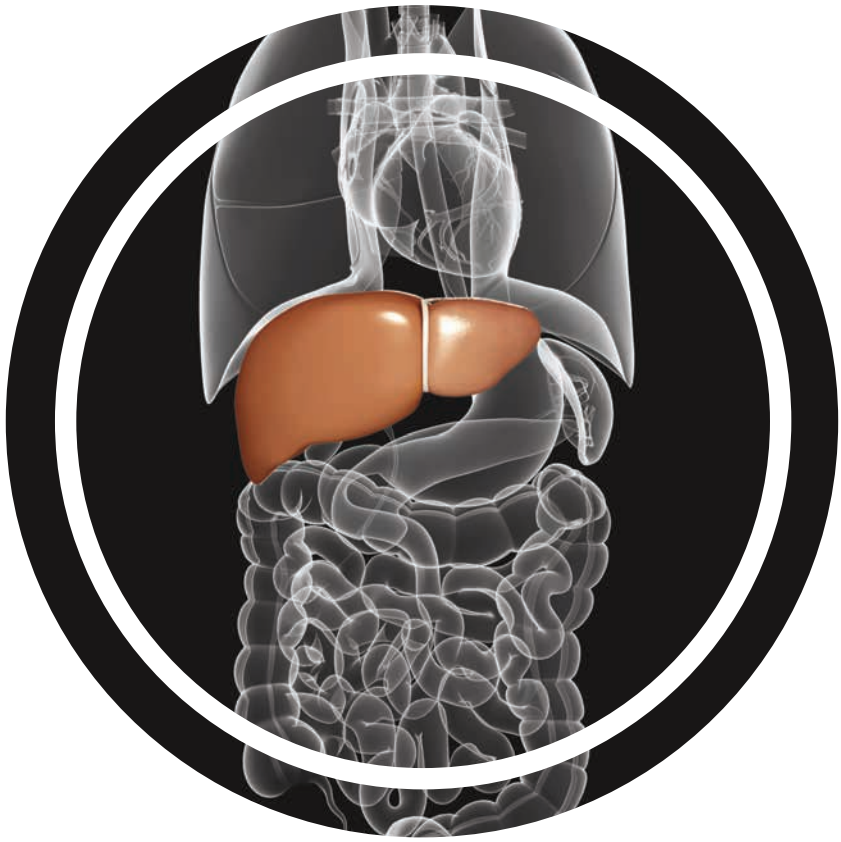
To make sure that you stay on track, Dr. Provenzale advised meeting with your mentor on a regular basis to redefine your goals, and finding ways to measure whether you are achieving them, either by completing tasks assigned to you, or delegating tasks to others when appropriate.

Finding some personal time daily for reading, writing, exercising – whatever floats your boat – is also essential to maintaining sanity and serenity.

Having contingency plans can also help, she added. For example, what happens if a grant you counted on does not come through, or if you face an unexpected family problem such as a sick child or aging parent?

And finding some personal time daily for reading, writing, exercising – whatever floats your boat – is also essential to maintaining sanity and serenity.

"Carve out time for yourself," Dr. Provenzale advised. "Enjoy the steps along the way as much as possible. As I reflect back over my career, many of the challenges I've faced have made me a better person and better able to help others." ■



Postfellowship Pathways: Advanced/Transplant Hepatology Fellowship

By Jennifer C. Lai, M.D., MBA

Jennifer Lai is assistant professor of medicine at the University of California, San Francisco, where she also completed her advanced/transplant hepatology fellowship.

What are the fellowship options available for someone interested in hepatology?

There are two fellowship options for gastroenterology fellows who are interested in gaining additional expertise in hepatology and liver transplantation. For the first option, fellows can seek a fourth year of training in hepatology and liver transplantation after completing three years of a gastroenterology fellowship. More recently, a second option has become available. GI fellows can obtain advanced hepatology training through a 1-year pilot hepatology fellowship during their third year of GI fellowship. Pilot fellows must complete all Accreditation Council for Graduate Medical Education (ACGME) requirements for GI fellows by the end of their second year of GI fellowship.

For the 2014-2015 academic year, there were a total of 46 hepatology fellows (36 fourth-year fellows, 10 pilot fellows) training in 43 transplant hepatology programs in the United States.

Both options provide specialized training in hepatology and liver transplantation that prepares physicians for advanced/transplant hepatology practice, such as treatment of chronic hepatitis C in the decompensated cirrhotic patient, evaluation of cirrhotic patients for liver transplantation, management of patients before and after liver transplantation, and treatment of hepatocellular carcinoma outside of Milan criteria.

After completing an advanced/transplant hepatology fellowship, physicians are eligible to sit for the Transplant Hepatology Boards offered by the American Board of Internal Medicine and administered every 2 years.

What does the transplant hepatology fellowship application process entail?

Application deadlines for transplant hepatology fellowships vary by program. There is no Match for advanced/transplant hepatology. In general, GI fellows interested in pursuing this additional training should contact transplant programs in the fall of their second year of GI fellowship. This time frame applies to both the fourth-year and the "pilot" fellowships. For example, at the University of California, San Francisco, applications for the 2017 fourth-year advanced/transplant hepatology program will be due around December 2015; applications for the 2016 pilot hepatology year will also be due December 2015.

What led you to pursue a transplant hepatology fellowship?

The clinical practice of inpatient transplant medicine is energizing. After I saw my first cirrhotic patient transform from being critically ill in the ICU with a MELD score of 40 to walking out of the hospital 7 days after his liver transplant, I was hooked. In my opinion, being a transplant hepatologist allows me to have the best of both worlds – I have the opportunity to establish long-term relationships with my patients and their families in the outpatient setting but also get the exhilaration of instantly changing the trajectory of a patient's life through transplant in the inpatient setting.

What was the most challenging aspect of your advanced/transplant hepatology fellowship?

It is an intense year for two major reasons. From a clinical perspective, managing inpatients for 6 months of the year (as required by the ACGME) can be exhausting, as decompensated cirrhotic patients in the hospital require constant attention. The stakes are high – one wrong move can mean the difference between transplant or death. As a trainee, I knew it was my last year to train under the experts, so I wanted to be involved with every decision possible so I could better prepare for entering clinical practice as an attending. This desire had to be balanced against the need to step away from the clinical arena to find a job after graduation, develop my research agenda, continue my research productivity, and apply for grants

After completing an advanced/transplant hepatology fellowship, physicians are eligible to sit for the Transplant Hepatology Boards offered by the American Board of Internal Medicine and administered every 2 years.

to support my research endeavors. Finding the balance between these seemingly competing interests was the most challenging aspect of the year.

How has your advanced/transplant hepatology fellowship benefited your career?

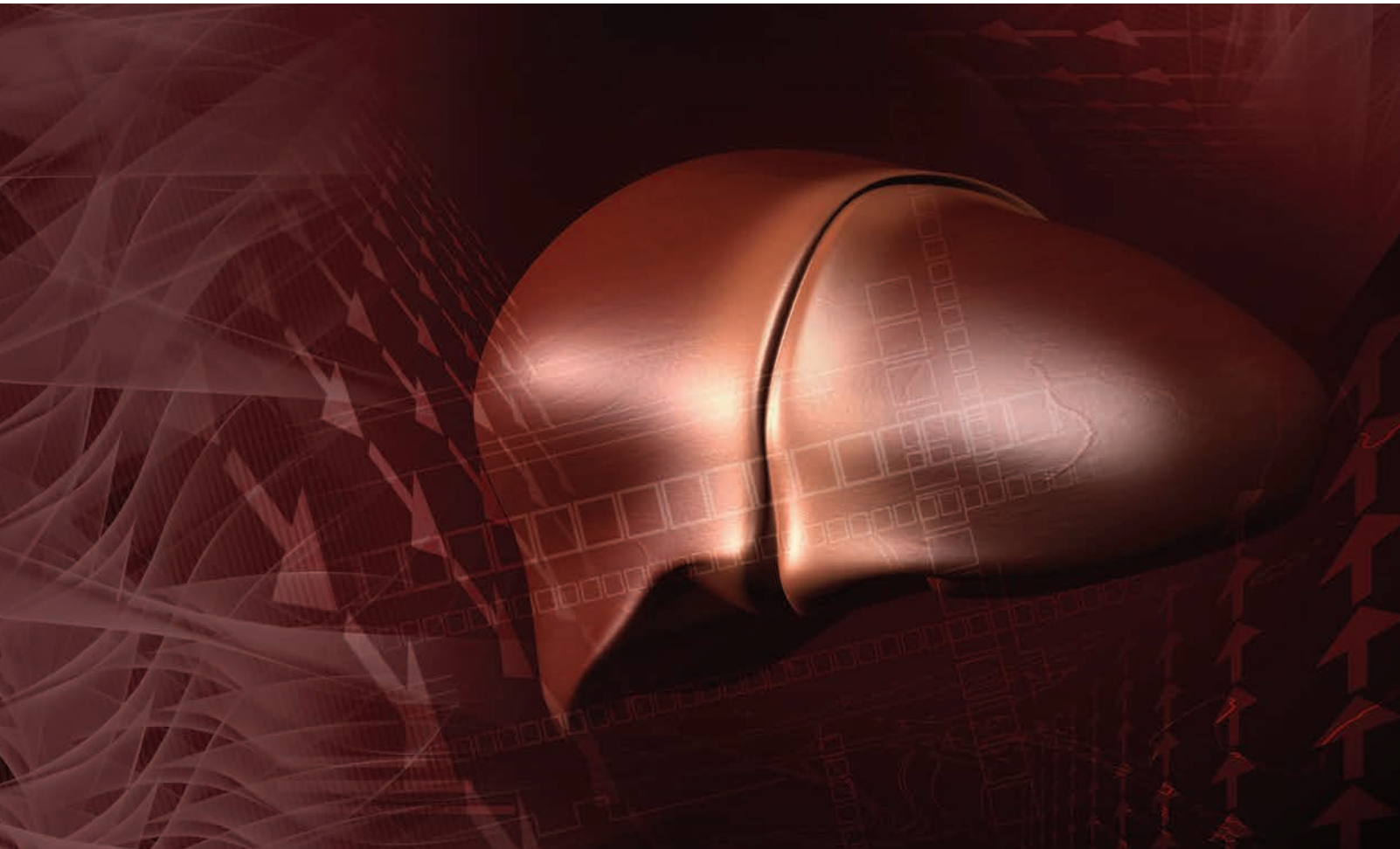
The training that I received during my advanced/transplant hepatology fellowship completely prepared me for real-life clinical practice. I was actively involved in the management of so many patients during the year that I felt that I had seen nearly everything that could happen to the liver. Of course, I hadn't actually seen *everything* in that one year, but the training that I received provided me with the foundation to approach the work-up and immediate management of acute liver failure, acute on chronic liver disease, and post-transplant complications.

Why would you recommend that young gastroenterologists pursue an advanced/transplant hepatology fellowship?

One of the greatest aspects of fellowship – whether it is advanced/transplant hepatology or gastroenterology – is the ability to learn from all of your attendings. It is a unique opportunity to see how different clinicians approach the same clinical problem and provides you with a range of options from which to choose when you go into clinical practice as an attending.

Do you think a advanced/transplant hepatology fellowship is necessary for young gastroenterologists who want to effectively treat liver disease in their practice?

This really depends upon the amount of exposure to managing chronic liver disease and its complications that trainees receive during their GI fellowship. At UCSF, where the advanced/transplant hepatology program is closely integrated into the GI fellowship, our GI fellows are trained to manage straightforward chronic liver diseases, cirrhosis, and its complications upon graduation. In this situation, I believe that they are prepared to manage liver disease in their gastroenterology practice and recognize when to refer to a hepatologist for additional expertise. However, even if a GI fellow obtains significant exposure to liver disease management, I recommend an advanced/transplant hepatology fellowship if she or he wants to manage more complex hepatology cases (e.g., chronic hepatitis C treatment in a decompensated cirrhotic patient, a patient with renal insufficiency, or with refractory autoimmune hepatitis) or to practice transplant hepatology. ■



Life Insurance for the Medical Professional

By Michael R. Mazzarella

Mr. Mazzarella is president of Physicians Consulting Group, LLC. The company has been assisting residents, fellows, and attending physicians with their life insurance and individual disability insurance planning at hospitals nationwide for over 20 years. Contact him at physiciansconsultinggroup@gmail.com

Single or married, young or old, many of us should have some sort of life insurance. But sifting through all of the information on life insurance can be confusing and complicated. This article will help you evaluate if you need life insurance, determine which type of insurance will best meet your needs, and guide you to the best life insurance coverage for your money.

Do you need life insurance?

Depending on where you are in your life and who you're responsible for, you could have any number of goals for your life insurance policy. Here are some of the most common goals for life insurance, which all have a bearing on how large a policy you might want:

- Covering end-of-life and funeral expenses
- Paying off debts, including a mortgage
- Allowing your family to maintain its lifestyle after you're gone
- Contributing to your child(ren)'s college fund
- Allowing your practice to continue operating without you
- Paying off the taxes and transfer expenses on your estate

Buying life insurance

When you buy life insurance, you want coverage that fits your needs. First, decide how much you need – and for how long – and what you can afford to pay. Keep in mind the major reason you buy life insurance is to cover the financial effects of unexpected or untimely death. Life insurance can also be one of many ways you plan for the future.

Next, learn what kinds of policies will meet your needs and pick the one that best suits you.

Then, choose the combination of policy premium and benefits that emphasizes protection in case of early death, or benefits in case of long life, or a combination of both.

It makes good sense to ask a life insurance agent or company to guide you through this process. An agent can help you review your insurance needs and give you information about available policies. If one kind of policy doesn't seem to fit your needs, ask about others.

What is the right kind of life insurance?

All policies are not the same. Some give coverage for your lifetime and others cover you for a specific number of years. Some build up cash values and others do not. Some policies may offer other benefits such as the accelerated death benefit rider and the critical illness rider while you are still living. Your choice should be based on your needs and what you can afford.

There are two basic types of life insurance: **term insurance** and **cash value insurance**. Term insurance generally has lower premiums in the early years but does not build up cash values that you can use in the future. You may combine cash value life insurance with term insurance to replace income in the event you cannot work/practice.

Term Insurance covers you for a term of 1 or more years. It pays a death benefit only if you die in that term. Term insurance generally offers the largest insurance protection for your premium dollar. It typically does not build up cash value.

You can renew most term insurance policies for one or more terms even if your health has changed. Each time you renew the policy for a new term, premiums may be higher. Ask what the premiums will be if you continue to renew the policy. Also ask if you will lose the right to renew the policy at a certain age. For a higher premium, some companies will give you the right to keep the policy in force for a guaranteed period at the same price each year. At the end of that time you may need to pass a physical examination to continue coverage and premiums may increase.

Return of Premium Term Insurance: As you might guess, this type of insurance gives you the option to get your premium back, minus fees and expenses, if you outlive your life insurance policy. These policies tend to come with much higher premiums, but can be a way to regain some money if you don't end up using your life insurance plan (i.e., you don't die during the term).

Cash Value Life Insurance is a type of insurance where the premiums charged are higher at the beginning than they would be for the same amount of term insurance. The part of the premium that is not used for the cost of insurance is invested by the company and builds up cash value that may be used in a variety of ways. You may borrow against a policy's cash value by taking a policy loan. If you don't pay back the loan and the interest on it, the amount you owe will be subtracted from the benefits when you die, or from the cash value if you stop paying premiums and take out the remaining cash value. You can also use your cash value to keep insurance protection for a limited time or to buy a reduced amount without having to pay more premiums. You also can use the cash value to increase your income in retirement or to help pay for needs such as your child's tuition without canceling the policy. However, to build up this cash value, you must pay higher premiums in the earlier years of the policy. Cash value life insurance include several types: whole life, universal life, and variable life.

Finding a good value in life insurance

After you have decided which kind of life insurance is best for you, compare

similar policies from different companies to find which one is likely to give you the best value for your money. A simple comparison of the premiums is not enough. There are other things to consider. For example:

- Do premiums or benefits vary from year to year?
- How fast does the cash value account accumulate?
- What part of the premiums or benefits is not guaranteed?
- What is the effect of interest on money paid and received at different times on policy? Remember that no one company offers the lowest cost at all ages for all kinds and amounts of insurance.
- How quickly does the cash value grow? Some policies have low cash values in the early years that build quickly later on. Other policies have a more level cash value build-up. A year-by-year display of values and benefits can be very helpful (the agent or company will give you a policy summary or an illustration that will show benefits and premiums for selected years).
- Are there special policy features that particularly suit your needs?
- How are nonguaranteed values calculated? For example, interest rates are important in determining policy returns. In some companies, increases reflect the average interest earnings on all that company's policies regardless of when they are issued. In others, the return for policies issued in a recent year, or a group of years, reflects the interest earnings on that group of policies; in this case, amounts paid are likely to change more rapidly when interest rates change.

Important things to consider

- Review your own insurance needs and circumstances. Choose the kind of policy that has benefits that most closely fit your needs. Ask an agent or company to help you.
- Be sure that you can handle premium payments. Can you afford the initial premium? If the premium increases later and you still need insurance, can you still afford it?
- Don't sign an insurance application until you review it carefully to be sure all the answers are complete and accurate.
- Don't buy life insurance unless you intend to stick with your plan. It may be very costly if you quit during the early years of the policy.
- Don't drop one policy and buy another without a thorough study of the new policy and the one you have now. Replacing your insurance may be costly.
- Read your policy carefully. Ask your agent or company about anything that is not clear to you.
- Review your life insurance program with your agent or company every few years to keep up with changes in your income and your needs.

To summarize, if it is important to you to protect your family's lifestyle, protect your business interest, or conserve your estate, this can all be accomplished with the proper life insurance policy. We recommend using a life insurance professional to help you with the process of selecting the policy type and amount that best suits your needs. With proper planning and sound advice from your life insurance broker you'll be able to prepare for the unexpected, which unfortunately is a part of life. ■

Established Career Profile: Dr. Loren Laine

By Kari Oakes

"Make sure to build research skills into your training. Find something you love doing. Make time for exercise and decompression."

These career and work-life balance tips for physicians beginning a challenging but rewarding career in gastroenterology come from Yale University's Dr. Loren Laine. Dr. Laine, a past President of the AGA and the recipient of multiple awards for clinical research from the AGA and the American College of Gastroenterology, spoke with *The New Gastroenterologist* recently. He discussed his early career, passion for clinical research, and shared advice for those entering the field.

Dr. Laine chose gastroenterology after completing medical school and residency at the University of California, Los Angeles, because the specialty requires both cognitive and procedural skills. With digestive issues, the physician has an opportunity to know an organ system well, and to understand how different disease processes impact health. "Gastroenterology, both then and now, represents a mix of diagnosis and treatment," he said.

He completed a gastroenterology fellowship at the University of California, San Diego. Early in his career, Dr. Laine became interested in gastrointestinal bleeding and has made it a primary focus for his clinical research. GI bleeds, he said, represent one of the few true emergencies in gastroenterology and present a challenge to gastroenterologists, emergency physicians, and hospitalists.

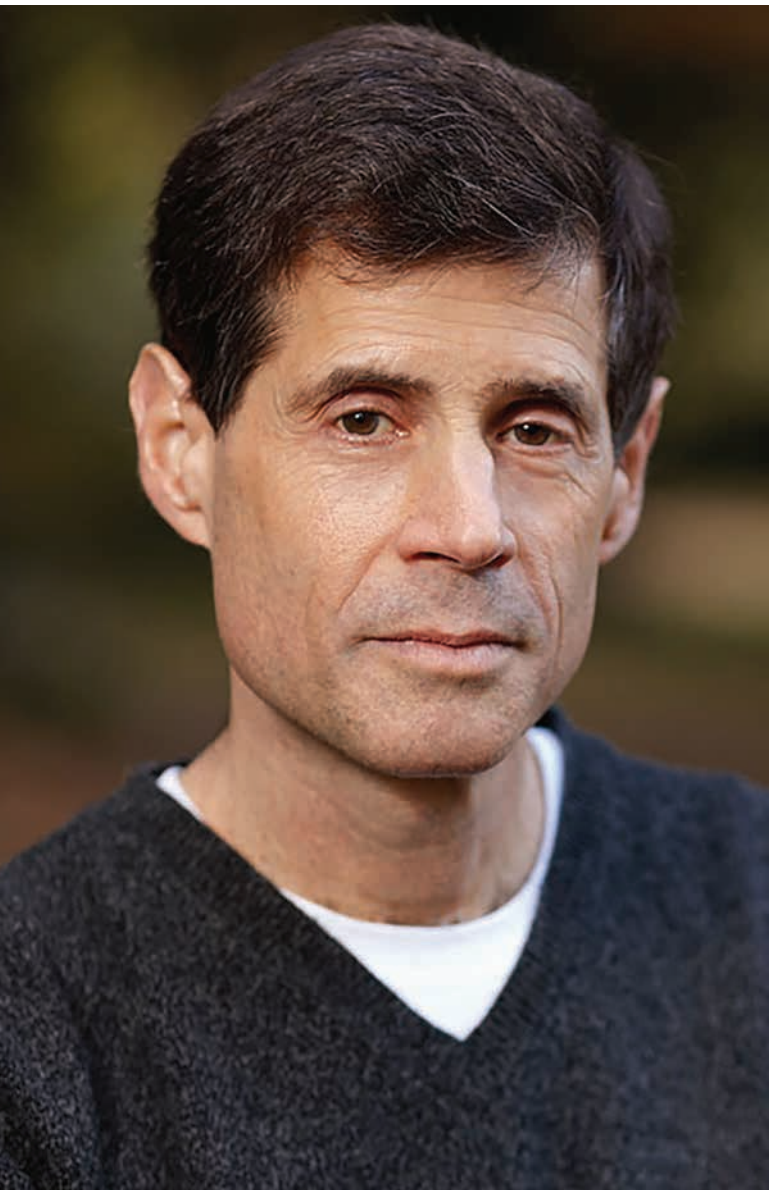
"Frankly, when I was starting, there was little or no evidence about what treatment was effective for GI bleeding," he said. He has found satisfaction in advancing medical knowledge and clinical interventions in an exciting area that is both important and clinically relevant.

Clinical research, he said, is the favorite part of his job. He especially loves the intellectual challenge of designing clinical trials and integrating his clinical practice into his research life. In fact, a key to his continued success in balancing clinical and research demands has been this integration: "I try to design trials where each patient I see could be considered as a potential research participant."

He also emphasized that clinical practice informs his research, and that he very much enjoys both the procedural and diagnostic challenges presented in the clinic.

As much as he loves his work, Dr. Laine acknowledged that it's still important to make room for relaxation,

With digestive issues, the physician has an opportunity to know an organ system well, and to understand how different disease processes impact health. "Gastroenterology, both then and now, represents a mix of diagnosis and treatment," [Dr. Laine] said.



Dr. Laine is professor of medicine in the section of digestive diseases at Yale University, New Haven, Conn.

and especially exercise, in the course of a work week. "I must admit I'm not always the best at work-life balance," said Dr. Laine. "But I really love what I do. I find clinical research engaging and fun, so sometimes it's hard to walk away from it." Luckily, Dr. Laine's four dogs provide him both with a distraction and an incentive to exercise.

When asked whether, in hindsight, he would choose the same career path again, Dr. Laine answered without hesitation, "Absolutely." However, he said, "The path is harder today for young gastroenterologists. It's harder than ever to balance clinical and research demands. With the focus on RVUs [Relative Value Units], clinicians have less leeway. You have to make the most of the bits of free time you can get."

Fellows who have an interest in research may find it harder than he did to achieve a balance between clinical and research obligations. "Now, it's hard – most models expect you to spend 80% or more of your time doing one or the other." Still, with some creativity, gastroenterologists can achieve a good balance between clinical research and practice.

"I must admit I'm not always the best at work-life balance," said Dr. Laine. "But I really love what I do. I find clinical research engaging and fun, so sometimes it's hard to walk away from it."

Dr. Laine advised physicians still in residencies or fellowships to build as much research training and experience as possible into this stage of their career. "Study design, statistical analysis, working with large datasets – all of these are really important and will help later on. I had to learn all of this on the job as I began doing more clinical research. If you know you're interested in doing research, acquiring those skills during training is really helpful."

Moving forward, Dr. Laine thinks that the greatest challenges presented to gastroenterologists over the next decade will come from American medicine's rapidly changing employment, documentation, and reimbursement models.

"We are seeing major changes in health care. We are changing from a fee-for-service, volume-based model of reimbursement. It's more and more important to document quality measures. We are going to see increased use of clinical decision tools with widespread adoption of electronic medical records and increased emphasis on evidence-based practice and quality metrics." Finally, it is his belief that more and more gastroenterologists will find themselves employees of a larger health care system. ■

IMPORTANT SAFETY INFORMATION

SUPREP® Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Most common adverse reactions (>2%) are overall discomfort, abdominal distention, abdominal pain, nausea, vomiting and headache.

Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Use can cause temporary elevations in uric acid. Uric acid fluctuations in patients with gout may precipitate an acute flare. Administration of osmotic laxative products may produce mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use. Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance.

BRIEF SUMMARY: Before prescribing, please see full Prescribing Information and Medication Guide for SUPREP® Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution. **INDICATIONS AND USAGE:** An osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. **CONTRAINDICATIONS:** Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. **WARNINGS AND PRECAUTIONS:** SUPREP Bowel Prep Kit is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Pre-dose and post-colonoscopy ECG's should be considered in patients at increased risk of serious cardiac arrhythmias. Use can cause temporary elevations in uric acid. Uric acid fluctuations in patients with gout may precipitate an acute flare. Administration of osmotic laxative products may produce mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use. Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance. **Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted. It is not known whether this product can cause fetal harm or can affect reproductive capacity. **Pediatric Use:** Safety and effectiveness in pediatric patients has not been established. **Geriatric Use:** Of the 375 patients who took SUPREP Bowel Prep Kit in clinical trials, 94 (25%) were 65 years of age or older, while 25 (7%) were 75 years of age or older. No overall differences in safety or effectiveness of SUPREP Bowel Prep Kit administered as a split-dose (2-day) regimen were observed between geriatric patients and younger patients. **DRUG INTERACTIONS:** Oral medication administered within one hour of the start of administration of SUPREP may not be absorbed completely. **ADVERSE REACTIONS:** Most common adverse reactions (>2%) are overall discomfort, abdominal distention, abdominal pain, nausea, vomiting and headache. **Oral Administration:** Split-Dose (Two-Day) Regimen: **Early in the evening prior to the colonoscopy:** Pour the contents of one bottle of SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount. Drink two additional containers filled to the 16 ounce line with water over the next hour. Consume only a light breakfast or have only clear liquids on the day before colonoscopy. **Day of Colonoscopy (10 to 12 hours after the evening dose):** Pour the contents of the second SUPREP Bowel Prep Kit into the mixing container provided. Fill the container with water to the 16 ounce fill line, and drink the entire amount. Drink two additional containers filled to the 16 ounce line with water over the next hour. Complete all SUPREP Bowel Prep Kit and required water at least two hours prior to colonoscopy. Consume only clear liquids until after the colonoscopy. **STORAGE:** Store at 20°-25°C (68°-77°F). Excursions permitted between 15°-30°C (59°-86°F). **Rx only**. Distributed by Braintree Laboratories, Inc. Braintree, MA 02185

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References: 1. IMS Health, NPA Weekly, March 2015. **2.** Rex DK, Di Palma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. *Gastrointest Endosc.* 2010;72(2):328-336. **3.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53. **4.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2012.

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