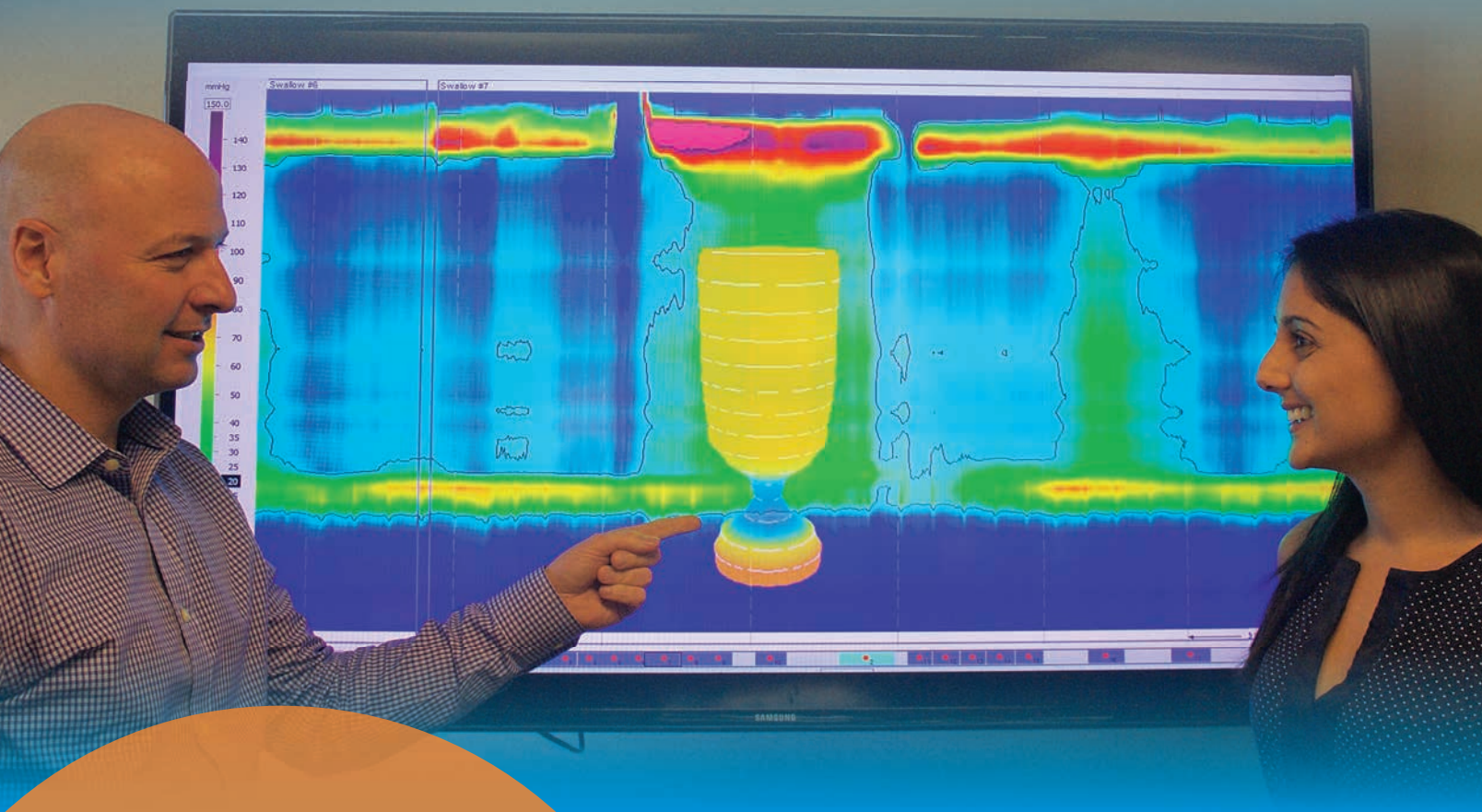
The NEW GASTROENTEROLOGIST

INSIGHTS FOR FELLOWS & YOUNG GIs

A Quarterly Supplement to GI & Hepatology News | Fall 2015



Achalasia Update

No Longer a Tough Diagnosis to Swallow

14

Letter
FROM THE EDITOR

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

Dear Colleagues,

In recent years the field of achalasia has advanced dramatically, with better understanding of the pathophysiology, improvement in disease classification with the use of high-resolution esophageal manometry, and the development of novel therapeutic approaches. In this fall issue of *The New Gastroenterologist*, Rena Yadlapati and John E. Pandolfino from Northwestern University provide a fantastic overview of the current state of achalasia, addressing epidemiology, pathophysiology, diagnostic criteria, and management.

In this issue's section on postfellowship pathways, Douglas S. Levine from Shire provides a useful perspective on a career in the biopharmaceutical industry and the opportunities for gastroenterologists in this field.

Also in this issue is an enlightening piece from Anne Peery, at the University of North Carolina, Chapel Hill, in which she discusses work-life balance. Additionally, we provide coverage of a recently published study that highlights the dilemma that physicians often face when dealing with their own illnesses. And, to address a topic that is constantly on the minds of most young career gastroenterologists, there is an informative overview of the basics of managing and repaying student loans, as well as many other features that I hope you will find both interesting and useful.

Please download our app, which is available free on iTunes, Google Play, and Amazon, or read our online edition, which is accessible through www.gastro.org or www.gihepnews.com. If you have any feedback about *The New Gastroenterologist*, or have ideas or contributions for future issues, please e-mail me at bryson.katona@uphs.upenn.edu or Erin Dubnansky at edubnansky@gastro.org.

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

The NEW GASTROENTEROLOGIST

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

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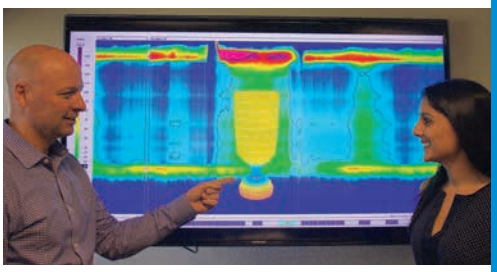
ON THE COVER

Dr. John E. Pandolfino and Dr. Rena Yadlapati of Northwestern University, Chicago.

Photo courtesy Dr. Rena Yadlapati

IN THIS ISSUE



DDSEP® 7
Digestive Diseases Self-Education Program®

QUESTIONS // Answers on page 27

Q1: A 60-year-old man presented with lightheadedness, fatigue, and ongoing melena. He had no significant prior medical history. He was hypotensive, and volume resuscitation was accomplished. A nasogastric tube was placed, and gross blood was aspirated. He was placed on a PPI drip. After the initial resuscitation, the patient was hemodynamically stable without respiratory distress. You were called, and an urgent endoscopy was planned. The following recommendation is the most likely to improve the endoscopic outcome:

A. Use iced-saline gastric lavage
B. Perform endotracheal intubation
C. Administer intravenous octreotide
D. Administer intravenous erythromycin
E. Start norfloxacin

Q2: A 32-year-old woman presents to clinic for evaluation of iron-deficiency anemia and hematochezia that has been attributed to hemorrhoids. On colonoscopy she is found to have a 3-cm ulcerated sigmoid adenocarcinoma and 30, 3 to 7-mm adenomas throughout the colon. She informs you that her sister was recently diagnosed with colorectal cancer at age 38 and had 8 adenomas on her first colonoscopy. Germline testing for an APC mutation is performed and is negative.

Which of the following is the best next step in this patient's evaluation?

A. Germline testing for mutations in MLH1, MSH2, MSH6, and PMS2 genes
B. No further genetic evaluation is necessary
C. Germline testing for mutations in STK11 gene
D. Germline testing for mutations in MUTYH gene
E. Tumor microsatellite instability testing

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

AGA Outlook

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

Upcoming Events

NOV 10, 2015
GI Boards

NOV 13-15, 2015
20th Annual Endoscopic Ultrasonography Live 2015
This course offers gastroenterologists, endoscopists, surgeons, and nurses an opportunity to review the indications and techniques used for EUS, fine-needle aspiration, and injection therapy.
Chicago, IL

DEC 10-12, 2015
2015 Advances in Inflammatory Bowel Diseases, Crohn's & Colitis Foundation's Clinical & Research Conference
Orlando, FL

FEB 5-6, 2016
Women's Leadership Conference — Experienced Track & Early Career Track
Apply to participate in the premier leadership development event that is tailor-made for women gastroenterologists.
Irving, TX

MAR 11-12. 2016
AGA-AASLD Academic Skills Workshop
This jointly sponsored workshop is designed to equip junior faculty and fellows with essential information to help them navigate and succeed in the highly competitive field of medical academia.
Phoenix, AZ

MAY 21-24, 2016
Digestive Disease Week® (DDW)
DDW® is the premier meeting for the GI professional. Every year it attracts approximately 15,000 physicians, researchers, and academics from around the world who desire to stay up-to-date in the field.
San Diego, CA

Awards Application Deadlines

Digestive Disease Week® (DDW) Abstracts
Deadline: December 1, 2015

AGA-Rome Foundation Functional GI and Motility Disorders Pilot Research Award
Deadline: January 15, 2016

AGA-Elsevier Pilot Research Award
Deadline: January 15, 2016

AGA-Elsevier Gut Microbiome Pilot Research Award
Deadline: January 15, 2016

AGA-Caroline Craig Augustyn & Damian Augustyn Award in Digestive Cancer
Deadline: January 29, 2016

AGA-Covidien Research & Development Pilot Award in Technology
Deadline: January 29, 2016

AGA Investing in the Future Student Research Fellowship
Deadline: February 5, 2016

AGA-Eli & Edythe Broad Student Research Fellowship(s)
Deadline: February 12, 2016

AGA/AGA-GRG Fellow Travel and Abstract of the Year Awards
Deadline: February 26, 2016

AGA-Moti L. & Kamla Rustgi International Travel Awards
Deadline: February 26, 2016

AGA Student Abstract Prizes
Deadline: March 4, 2016

What's Your Diagnosis?

Severe diarrhea following bone marrow transplantation is not always caused by GVHD

Published previously in Gastroenterology (2014;146:e5-6)

By Giovanni De Petris, M.D., Alexandra Corominas Cishek, M.D., and Ivana Dzeletovic, M.D.

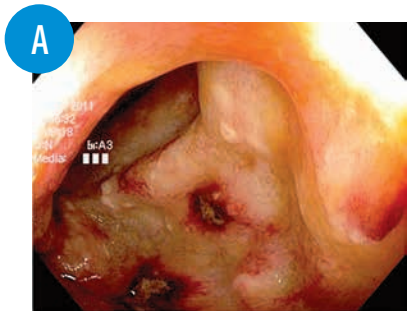
A 35-year-old man complained of persistent diarrhea 40 days after bone marrow transplant. Esophagogastroduodenoscopy (EGD) and biopsies showed graft-versus-host disease (GVHD) grade IV (of Lerner) and gastric ulcers with cytomegalovirus (CMV) infection. Biopsies from the colonoscopy showed GVHD (histologically compatible with grade II of Lerner). The patient was treated and showed improvement of his symptoms but diarrhea persisted.

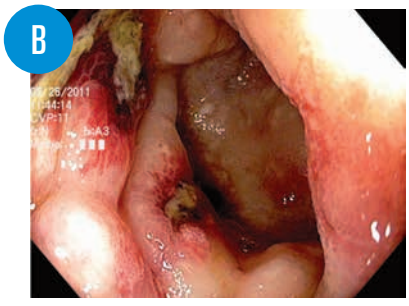
Follow-up EGD presented diffuse improvement of the erythema in stomach and duodenum; the colonoscopy was normal. The pathology in each site showed no evidence of GVHD or CMV, and regenerative changes of the mucosa. Four days later, worsening of symptoms occurred despite treatment, with severe diarrhea (4 L/d), intermittently bloody, and mild abdominal pain.

The laboratory results were hemoglobin, 10 g/dL; white blood cell count, 2,000 cells/microL; platelets, 60,000/microL; blood urea nitrogen/creatinine, normal; mild electrolyte abnormalities; lactate dehydrogenase, 450 U/L; and blood film, pancytopenia, no circulating lymphoma cells, no schistocytes. Colonoscopy (Figures A and B) with the lesions depicted present throughout the colon and the colon biopsies histology (Figures C and D) are shown. ■

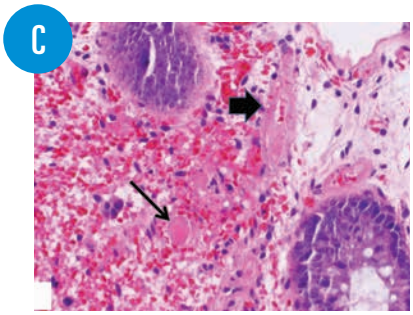
What is this condition?

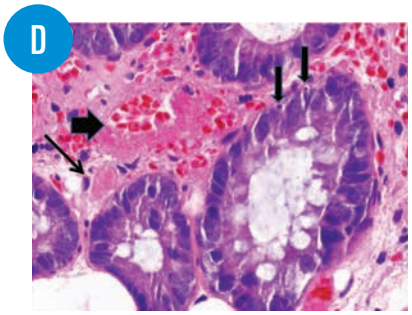
Dr. De Petris and Dr. Corominas Cishek are in the Department of Pathology, Mayo Clinic in Arizona, Scottsdale; and Dr. Dzeletovic is in the Department of Gastroenterology, Mayo Clinic in Arizona, Scottsdale.





See ***The Answer*** on page 30





News from the AGA

AGA Proposes Eliminating Secure Exam for MOC

Frustrated by a maintenance of certification process that didn't improve patient care, AGA convened a task force to propose an ideal pathway for recertification. The AGA proposal, unveiled online this August in both *Gastroenterology* and *Clinical Gastroenterology and Hepatology*, eliminates the high-stakes examination and replaces it with active and adaptive learning self-directed modules that allow for continuous feedback, and are based solidly on learning theory.

Read the full proposal, Bridging the G-APP: Continuous Professional Development for Gastroenterologists: Replacing MOC with a Model for Lifelong Learning and Accountability, at http://www.gastrojournal.org/article/S0016-5085(15)01177-4/pdf, and the editorial, An Alternative to MOC?, at http://www.gastrojournal.org/article/S0016-5085(15)01178-6/pdf (log-in required). The proposal will be available in the November print issues of *Gastroenterology* and *Clinical Gastroenterology and Hepatology*.

Provide feedback to AGA on our survey page (www.surveymonkey.com/s/gappfeedback).

"There is now a greater emphasis than ever before on disease pathways, clinical guidelines, and quality improvement, making it important for physicians to remain current with newer recommendations and practice standards," said Dr. Michael Camilleri, President, AGA Institute. "Maintaining certification should be a process of active learning, not high-stakes testing."

Three things to know about AGA's Alternate Recertification Pathway:

- Individual self-assessment pathways allow physicians to achieve a high level of competency in one or more areas, while maintaining a general level of competency in other areas.
- Individualized self-assessment activities provide constant feedback and opportunities for learning and replace the high-stakes exam now required every 10 years.
- Physicians get credit for activities they are already doing in practice, research, or teaching.

For more information, watch a quick video introduction (https://www.youtube.com/watch?v=5hV70RlxP3Y) by Dr. Suzanne Rose, MSEd, AGAF, Education and Training Councillor on the AGA Institute Governing Board. We do not expect the process to change overnight, but we're getting the conversation started in a substantial, meaningful way. AGA supports continuous education and professional development that enhances patient care.

Thanks to AGA members who served on the task force:

Suzanne Rose, M.D., MSEd, AGAF
Brijen J. Shah, M.D.
Jane Onken, M.D., MHS, AGAF
Arthur J. DeCross, M.D., AGAF
Maura H. Davis
Rajeev Jain, M.D., AGAF
Lawrence S. Kim, M.D., AGAF
Kim Persley, M.D.
Sheryl A. Pfeil, M.D., AGAF
Lori N. Marks, Ph.D. ■

AGA Fights for Fair Colonoscopy Reimbursement

Earlier this summer, CMS proposed drastic cuts to the 2016 Medicare physician reimbursement rates for colonoscopy and other lower GI endoscopy procedures. AGA, in coordination with ACG and ASGE, is fighting for fair and accurate reimbursement for all lower endoscopy procedures, including colonoscopy.

Some good news – we have the support of some important members of Congress. Representatives Donald Payne Jr. (D-NJ) and Leonard Lance (R-NJ) have asked their colleagues in the U.S. House of Representatives to join them in expressing concern over two key issues:

- Recently proposed Medicare payment cuts to colonoscopy.
- Impact of the cuts on access to colorectal cancer screening, especially in light of recent gains made in access to this life-saving procedure.

AGA members have been critical in this fight. More than 550 members participated in our poll on colonoscopy pay cuts; the results of which were presented to CMS by AGA, ACG, and ASGE during a meeting in July. We also garnered the support of more than 300 gastroenterologists who reached out to CMS about how these cuts will affect their patients and practice. We thank you for your help on this important issue.

We expect the final rule to be released later this month. Stay tuned to your email and AGA eDigest for continuous updates on this important matter. ■

Workshop Provides Insight on Building a Career in Academic Medicine

Trainees and junior faculty are encouraged to submit an application for an opportunity to attend the AGA-AASLD Academic Skills Workshop, taking place March 11 and 12, 2016, in Phoenix, AZ. This is a chance to get insight from accomplished academicians on what it takes to successfully shape a career in academic medicine. Not only will participants be able to better understand academic processes, they'll also develop the skills necessary to help position themselves for future success.

The workshop will address topics such as:

• Your first academic job – Learn how changes in health care reimbursement are impacting academic medicine and discover how to manage personal and workplace expectations.

• Academic medicine: tracks and pathways – Learn about available opportunities and strategies that can lead to future promotions.

• How to be a successful mentee – Find out how to get the most out of your mentor-mentee relationship to help with achieving short- and long-term goals.

• Writing and presentation skills – Acquire tips and strategies for writing grants and preparing, editing, and submitting manuscripts.

• Career development: strategy and funding – Get information on early career funding opportunities, including grants available for young investigators.

Forty candidates will be selected to participate in the workshop and all interested candidates must be a member of either AGA or AASLD. Women and underrepresented minorities are strongly encouraged to apply. Applications are due no later than Monday, Oct. 26, 2015.

Learn more about the AGA-AASLD Academic Skills Workshop at http://www.gastro.org/in-person/2016/3/11/aga-aasld-academic-skills-workshop and apply today. ■

AGA Guidelines Patients Can Understand

To help patients better understand the latest clinical information presented in AGA guidelines, AGA has started creating patient guideline summaries that:

• Provide information for patients on the clinical issue addressed by the guideline.

• Explain the recommendations and their impact on patient care.

• Pose helpful questions for patients to ask their gastroenterologists related to the guideline.

The patient guideline summaries support physicians in their efforts to effectively communicate important information to their patients and empower the patient and physician to work together to make the most informed and appropriate care decisions possible. As they are published, the patient guideline summaries will be available in *Gastroenterology* and on the AGA website (http://www.gastro.org/patient-care/patient-center). Current patient summaries include:

• Crohn's disease drugs.

• HBV reactivation.

• IBS drugs.

• Pancreatic cysts.

AGA has a rigorous guideline development process that develops focused, actionable clinical recommendations based on in-depth reviews of all available evidence.

To supplement the robust portfolio of guidelines, each new guideline is supplemented by a clinical decision support tool, an illustrated algorithm based on the evidence presented in the technical review, and a patient summary. These tools can be used at the point of clinical care to help with rapid decision making. ■

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Repaying Your Student Loans: Tips for Making Smart Decisions

By Jay M. Weinberg, CLU, ChFC, and Aaron Braunstein

Mr. Weinberg and Mr. Braunstein are financial planners with Atlantic Pension Planning Corp., whose practices primarily assist physicians and dentists. Mr. Weinberg can be reached at jay@atlanticpension.com; Mr. Braunstein at aaron@atlanticpension.com.

Student loans are an important part of financial planning for physicians and therefore require proper management. In this article we will lay out several key considerations of student loans that will guide you toward smart decisions for your financial future.

What is the difference between federal loans and private loans?

Typically, federal loans have more flexible repayment options and potential forgiveness. However, many private loan refinance options now offer significantly lower interest rates than existing federal loans.

Is the interest paid on student loans tax deductible?

If you are single and your modified adjusted gross income is less than $80,000 or you are married and earn less than $160,000 combined, all or some of your interest paid – with a cap of $2,500 – is deductible. These figures can change annually, so it is best to refer to IRS publication 970 for the most up-to-date information.

How does the interest rate on a student loan impact your strategy towards paying it off?

Naturally, it is always advantageous to pay off the higher interest rate loans before the lower interest rate loans. However, there are additional factors to consider when developing a plan to pay off your loans:

- Are the loans federal or private?
- Are you planning to be eligible for a forgiveness program?
- What is your overall loan balance?
- Do you expect your income to increase over time or could it have major fluctuations?

Are all federal loans the same?

No. When you took out the loan, what the loan was for, and what your financial need was at the time of the loan will dictate the type of government loan that you have. The three common federal loan types are Stafford, Perkins, and Plus. For more information about these types of loans, visit www.studentloans.gov/myDirectLoan/index.action.

What are the most common federal repayment strategies?

- Income Based Repayment (IBR) – Generally, 15% of your discretionary income.
- Pay As You Earn (PAYE) – 10% of your discretionary income.
- Standard Repayment – You have a maximum of 10 years to pay off the outstanding principal and interest of the loan.
- Extended Repayment – You have a maximum of 25 years to pay off the outstanding principal and interest of the loan.

Some considerations to keep in mind about these repayment strategies include:

- There are no prepayment penalties for government loans; therefore, you have the ability to pay "extra" money toward these loans to pay them off sooner.
- As your income increases, so will the monthly payments on your IBR and PAYE. However, the monthly payment on your IBR and PAYE will never exceed your Standard Repayment.
- Not all borrowers are eligible for PAYE currently; however, by the end of 2015 we expect that all borrowers with "Direct Loans" will be eligible. Direct loans are those made directly by the U.S. Department of Education. PAYE is the most advantageous plan if you expect to be eligible for various forgiveness programs, as this option will require the lowest out-of-pocket payment.

What is Public Service Loan Forgiveness (PSLF)?

In October 2007, the PSLF program was introduced by the U.S. Government under the College Cost Reduction and Access Act of 2007 (CCRAA). This program offered forgiveness to individuals that make 120 qualifying payments on "Direct Loans." There are many government or not-for-profit institutions that are eligible, but we highly recommended that you verify, in advance, that your current employer fits the qualifications. There is a lot of uncertainty related to caps on forgiveness amounts and eligibility requirements surrounding PSLF; therefore, it is important that you keep up to date on proposed changes coming from our government.

There are no prepayment penalties for government loans; therefore, you have the ability to pay "extra" money toward these loans to pay them off sooner.

Is it better to pay the minimum on loans or aggressively pay them off?

If you are hoping to be eligible for a forgiveness program, there is no reason to "overpay" now on your loans only to have the balance forgiven at some point in the future. On the contrary, if a forgiveness program is not

an option, the interest rates on your loans will dictate how aggressively you should pay them off.

What is a private loan refinance and does it make sense?

In the past few years, several private (nongovernment) lenders have entered into the student loan refinance market and offer repayment terms that are far more favorable than the 6%, 7%, or 8% interest rates attached to government loans.

A private loan refinance is not for everybody. If you expect to be eligible for one of the many forgiveness programs, it may not be for you. However, if you have high-interest-rate government (or private) loans and are not eligible for any forgiveness programs, you should absolutely consider the pros and cons of refinancing all or some of your existing loans. Interest rates on private refinances can be as low as 2%, but are typically 3%-6%. You have the choice of a variable interest rate or a fixed interest rate. Repayment terms are generally from 5 to 20 years.

We have received extremely favorable feedback about two private lenders in particular: SOFI (Social Finance) and DRB (Darien Rowayton Bank). If you are contemplating a refinance, we encourage you to contact both of these lenders and compare offerings. There are links at the end of this article that offer bonuses if you refinance with either of these companies.

Should I consolidate my federal loans?

Prior to 2006, it was advantageous to consolidate federal loans because it significantly lowered interest rates. Since then, the federal consolidation landscape has changed. If you do a federal consolidation today, the interest rates on all of the consolidated loans are averaged together. Chances are that engaging in a federal consolidation will not save you money; it will simply make record keeping easier. If you do a consolidation and extend the payment period of the loan, you may actually pay more money in interest over time compared to if you did not consolidate. It is important to know that a consolidation is one of the ways to get out of "default" and get back into a current repayment plan.

Can I refinance some, but not all, of my loans?

Yes, you can selectively pick which loans you want to "leave alone" and which loans you want to refinance or consolidate.

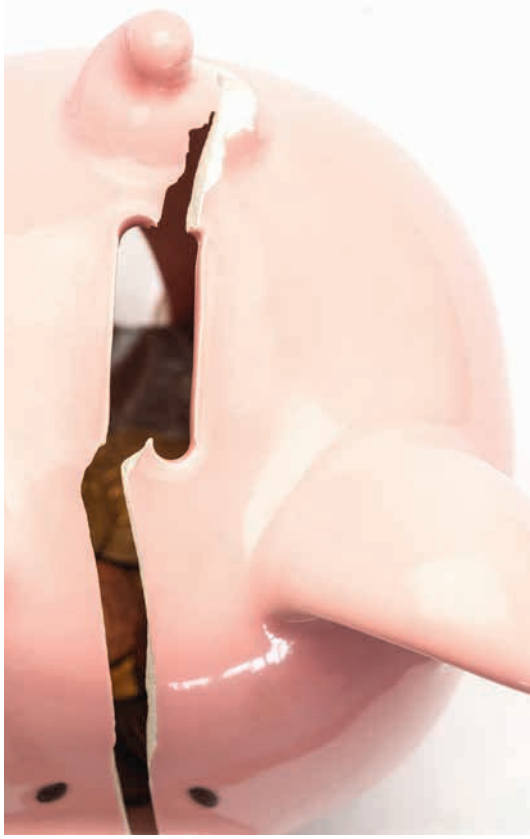
If I get into a bind with my loans, what should I do?

We always recommended that you contact the servicer of your loan to find out what your options are. If you come upon a financial hardship, there may be some relief available but you need to ask for help in order to receive it. During a medical residency, forbearance is an option on your federal loans. In fellowship, deferment is an option for your federal loans.

Should I pay off my loans before purchasing a home?

There is no "right" answer to this question; however, there are certain factors that you need to take into account when weighing the options. What is the interest rate on the student loans? Are you eligible for a tax deduction of $2,500 for student loan interest? What interest rate would the home mortgage be? What tax bracket are you currently in and do you see yourself being in over the next 5 or 10 years? How will the student loans be counted toward your debt-to-income ratios to qualify for a mortgage approval?

Most people would rather borrow as much money as they can at 3% or 4% (tax deductible) toward the purchase of a home and use current savings and cash flow to pay off high-interest-rate student loans (few or no tax benefits). No two situations



are the same and we recommend that you weigh your options and decide which plan best suits your goals.

Developing a plan for either paying off your student loans or making yourself eligible for a forgiveness program are important steps toward the makings of a bright financial future. There are many resources available to borrowers and taking a proactive approach toward managing your student loans will certainly benefit your situation over time. ■

Resources:

https://studentloans.gov/myDirectLoan/index.action – Federal Student Aid – U.S. Dept. of Education

https://www.aamc.org/advocacy/meded/79048/student_loan_repayment.html – American Association of Medical Colleges

http://www.direct.ed.gov/calc.html – Loan Calculators and Interest Rates

http://pgpresents.com/ – Student Loan Consulting – Paul Garrard

http://sofi.com/AtlanticPensionPhysicians – SOFI – Link to refinance and receive $200 welcome bonus

https://student.drbank.com/?provider=jwapp – DRB Education Refinance – Link to refinance and receive $200 referral bonus

Snapshots from the AGA Journals

Cefazolin Ranks Sixth as Cause of Drug-Induced Liver Injury

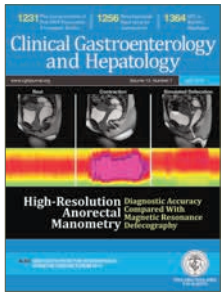
July Clinical Gastroenteology and Hepatology (doi: 10.1016/j.cgh.2015.01.010]

Key clinical point: A single dose of cefazolin can cause drug-induced liver injury (DILI), and the agent is implicated more often than previously thought.

Major finding: Cefazolin ranked sixth among causes of DILI, and signs and symptoms began 1-3 weeks after initial exposure.

Data source: Registry-based study of 1,212 cases of DILI.

Disclosures: The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, the National Cancer Institute, and by Clinical and Translational Science Award grants. The investigators reported having no conflicts of interest.



Commentary

Dr. Stuart Gordon is professor of medicine at Wayne State University School of Medicine and director of the Division of Hepatology at Henry Ford Health Systems, Detroit. He has no relevant conflicts of interest.

The investigators from the Drug-Induced Liver Injury Network (DILIN) report a previously unrecognized phenomenon: Patients who receive a single dose of an IV cephalosporin prior to an operative procedure may develop jaundice and biochemical cholestasis 1-3 weeks later. Remarkably, every single patient in this case series also presented with pruritus, suggesting an allergic reaction. Nearly half of the patients reported a previous "drug allergy" (although it is uncertain whether this was disclosed before their procedures), and some were in fact penicillin allergic, so likely should not have ever received cefazolin.

Some of the late-onset cases described in this series could have justified a misdiagnosis of "postoperative cholestasis" or have led to a fishing expedition for various "zebra" diagnoses. What is instructive in this report is that, for the most part, neither the patients nor the doctors evaluating their unexplained hepatitis ever suspected that an antibiotic had even been given. This observation highlights the fact that often medications that are used just once in the surgical suite will then disappear from a patient's medications list and are often difficult to subsequently identify in the electronic medical record.

Cefazolin is the workhorse for preoperative prophylaxis in cardiac and orthopedic surgery, and most operations involving skin, such as plastic surgery. Such antibiotic prophylaxis is generally used very appropriately and according to evidence-based clinical guidelines, and it is a closely monitored and audited quality indicator at hospitals and surgical centers. The use of intravenous cefazolin as preoperative prophylaxis will likely not be diminished by these reports, but this case series again emphasizes the need to avoid cephalosporins among patients who report previous beta-lactam allergies. Early recognition of this culprit in cases of unexplained cholestatic hepatitis, especially in patients who recently underwent operative procedures, may obviate hospitalization. ■

Pentoxifylline Beat Placebo in Acute Pancreatitis Trial

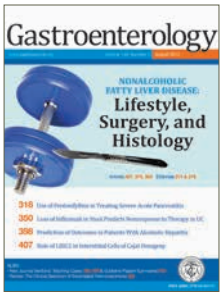
August Gastroenterology (doi:10.1053/j.gastro.2015.04.019)

Key clinical point: Pentoxifylline topped placebo among patients with severe acute pancreatitis.

Major finding: The pentoxifylline treatment group had significantly fewer hospitalizations requiring more than 4 days (14% vs. 57% for the placebo group; $P = .046$) and a significantly shorter median duration of stay in the ICU ($P = .03$).

Data source: A single-center, randomized placebo-controlled trial of 28 patients with predicted severe acute pancreatitis.

Disclosures: A scholarly opportunity award from the Mayo Clinic supported the work. The investigators reported having no relevant financial conflicts of interest.



Commentary

Dr. Matthew J. DiMagno is in the division of gastroenterology and hepatology, department of internal medicine, University of Michigan, Ann Arbor. He serves as chair of the American Gastroenterological Association Institute Council Section on Pancreatic Disorders. He declared no relevant financial conflicts of interest.

The study of acute pancreatitis (AP) is economically and scientifically essential because acute pancreatitis is the most common reason for hospitalization among patients with GI diseases, consumes considerable resources, and is treated primarily with supportive measures. The pilot study by Dr. Vege and his colleagues reports that pentoxifylline treatment is safe for patients with severe acute pancreatitis and is associated with a promising reduction in ICU utilization and duration in patients requiring a hospital stay > 4 days.

This study not only is provocative but also raises the hypothesis-generating question of how pentoxifylline might exert a salutary effect without reducing blood tumor necrosis factor–alpha levels (or IL-6, IL-8, or C-reactive protein levels). The authors ascribe this discordance to the timing of administering pentoxifylline and to potential TNF-alpha independent effects. Biologically, pancreatic TNF-alpha levels increase within the first 30-60 minutes of onset of acute pancreatitis (Am. J. Surg. 1998;175:76-83). In experimental AP, pentoxifylline ameliorates severity, but data are conflicting about whether prophylactic or delayed (Surgery 1996;120:515-21) antagonism of TNF-alpha signaling is more protective. Clinically relevant data suggest that prophylactic administration of pentoxifylline does not prevent postendoscopic retrograde cholangiopancreatography pancreatitis (Gastrointest. Endosc. 2007;66:513-8), but nonprophylactic administration of pentoxifylline improves short-term survival in alcoholic hepatitis without significantly reducing blood TNF-alpha levels (Gastroenterology 2000;119:1637-48). Hence, pentoxifylline appears to ameliorate AP and alcoholic hepatitis through TNF-alpha independent signaling, conceivably by targeting the microcirculation, as described for patients with claudication (Angiology 1994;45:339-45).

Future studies might test this hypothesis by determining whether pentoxifylline blunts increases in deleterious vascular factors (for example, angiopoietin-2) [Am. J. Gastroenterol. 2010;105:2287-92; J. Am. Coll. Surg. 2014;218:26-32; Am. J. Gastroenterol. 2011;106:1859-61]) and reduces vascular complications that correlate with the need for ICU care and more severe AP. ■

Circulating Tumor DNA Marked Progressive Liver Cancer

September Cellular and Molecular Gastroenterology and Hepatology (doi: 10.1016/j.jcmgh.2015.06.009)

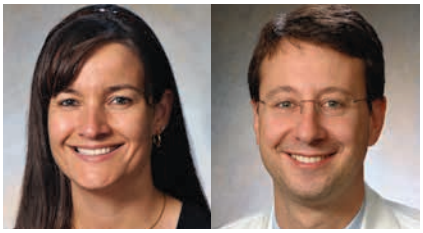
Key clinical point: The presence of circulating tumor (ct) DNA indicated progression of hepatocellular carcinoma.

Major finding: Among seven patients who tested positive for ctDNA before undergoing surgical resection, six developed recurrent HCC and four developed extrahepatic metastases.

Data source: Real-time quantitative PCR analysis of serum samples from 46 patients with HCC who underwent hepatectomy or liver transplantation.

Disclosures: The study was funded by the government of Japan, the RIKEN President's Fund, the Princess Takamatsu Cancer Research Fund, and the Takeda Science Foundation. The investigators declared no competing interests.

Commentary



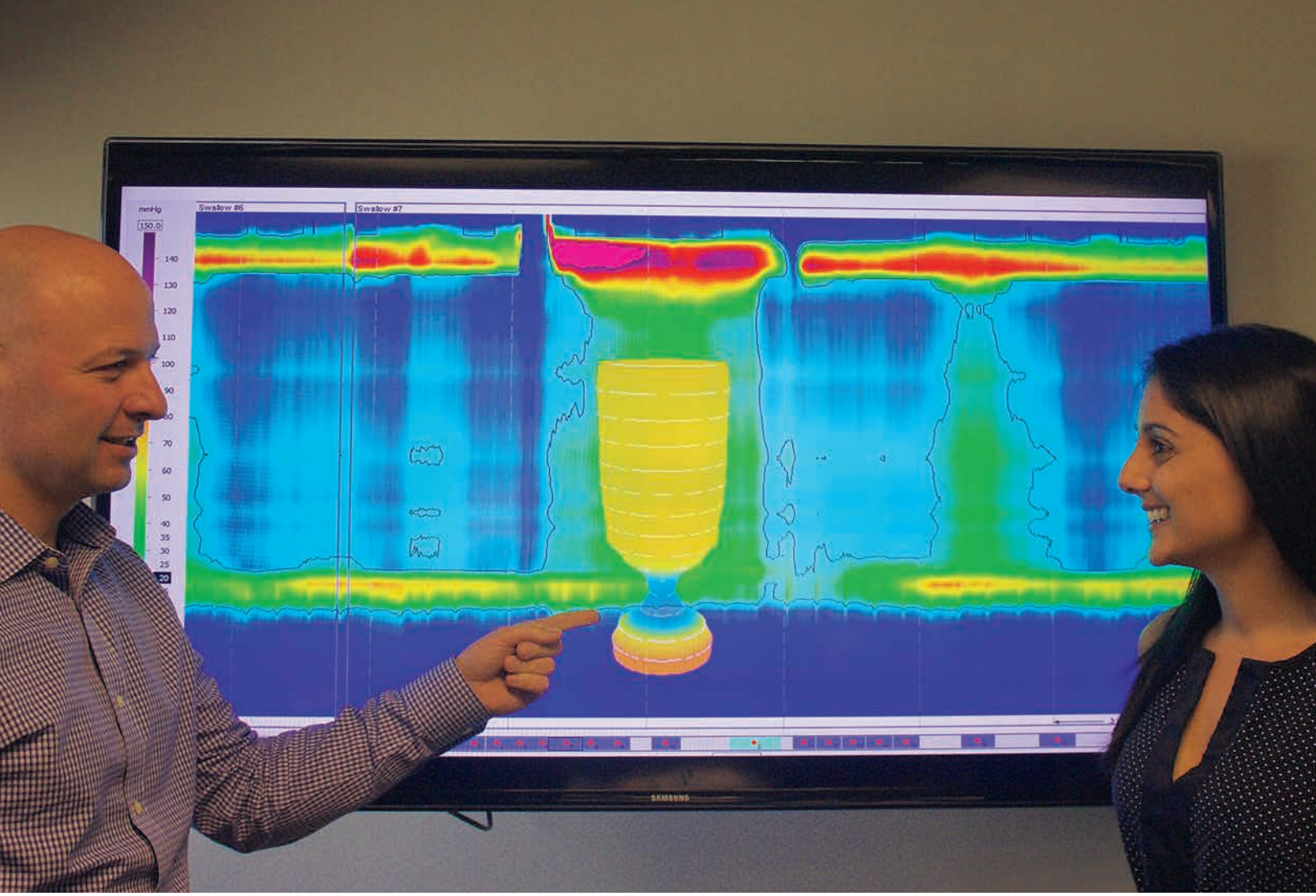
Dr. Larissa V. Furtado and Dr. Jeremy P. Segal are both assistant professors and assistant directors of the division of genomic and molecular pathology in the department of pathology at the University of Chicago Medical Center. Neither has any conflicts of interest.

As the oncology field advances toward implementation of personalized medicine programs, molecular and genomic analysis of circulating tumor DNA (ctDNA) represents a promising approach for diagnosis, prognosis, therapy selection, and minimal residual disease monitoring of a wide array of malignancies.

With the purpose of assessing the utility of extracellular tumor DNA as a potential biomarker for hepatocellular carcinoma (HCC), Dr. Ono and colleagues analyzed serum ctDNA from 46 HCC patients using quantitative PCR assays for somatic rearrangements uncovered by whole-genome sequencing of their primary tumors.

For the seven patients with detectable ctDNA in preoperative serum, the incidence of recurrence and extrahepatic metastasis within 2 years following hepatectomy were significantly worse than in the ctDNA-negative group, although no significant difference in the cumulative survival rate was observed between these patients. The ctDNA positivity also was found to be an independent predictor of microscopic vascular invasion of the portal vein, and it correlated with larger tumor size and higher alpha-fetoprotein and des-gamma-carboxy prothrombin levels.

In addition, the investigators demonstrated that transcatheter arterial chemoembolization enriched ctDNA levels in cell-free DNA in blood, and that serum ctDNA levels were increased with disease progression and reflected response to treatments. The diagnosis of HCC is currently based on imaging and/or biopsies. Even though there are no well-established biomarkers for early detection and monitoring of HCC at present, the data presented here indicate the potential utility of personalized ctDNA testing for individualized management of hepatocellular carcinoma patients. ■



Courtesy Dr. Rena Yadlapati

Achalasia Update: No Longer a Tough Diagnosis to Swallow

By Rena Yadlapati, M.D., and John E. Pandolfino, M.D., M.S.

Dr. Yadlapati is a fellow and Dr. Pandolfino is the chief of the division of gastroenterology and hepatology, Northwestern University, Chicago.
Dr. Yadlapati is supported by grant T32 DK101363-02.

Historical perspective
The medical field first recognized achalasia in 1674 when Sir Thomas Willis described the use of a carved whalebone with a sponge at the distal end as management for his patient with liquid dysphagia, at the time referred to as cardiospasm.[1] In the late 1920s, this disease entity was renamed achalasia, a term derived from the Greek *khalasis,* meaning "not loosening or relaxing."[2,3] Over the past century, the diagnostic understanding and management strategies for achalasia have significantly evolved.

Epidemiology and pathophysiology
Achalasia presents at an estimated annual incidence of 1.6 in 100,000 and a prevalence of 10.8 in 100,000 without a racial or gender predilection.[4] While its peak incidence occurs between the ages of 30 and 60, achalasia can present at any age.[5] A defining feature of achalasia is impaired deglutitive relaxation of the lower esophageal sphincter (LES), considered to be a result of the functional loss of the myenteric plexus. While the precise cause of neuronal degeneration is unknown, it is thought to be multifactorial, involving an autoimmune process triggered by an indolent viral infection in conjunction with a genetically susceptible host.[6] Normally, the postganglionic neurons use nitric oxide and vasoactive intestinal polypeptide as inhibitory neurotransmitters. In the setting of myenteric degeneration there exists an imbalance between excitatory and inhibitory neurons, with the unopposed cholinergic stimulation resulting in impaired LES relaxation and distal esophageal dysmotility.[7] Infection by *Trypanosoma cruzi*, known as Chagas disease, can also manifest with achalasia in addition to other features of widespread myenteric plexus destruction, including megacolon, heart disease, and neurologic disorders.[5,6,8]

Clinical presentation
The hallmark symptom of achalasia, present in 90% of cases, is a progressive constant dysphagia of both solids and liquids. Other common esophageal symptoms include heartburn, noncardiac chest pain, regurgitation, odynophagia, and epigastric pain.[9,10] Additionally, patients with achalasia can present with cough, asthma, and chronic aspiration. Over time, patients learn to adapt to their dysphagia by modifying their dietary habits and becoming "slow eaters." Unintentional weight loss may not present until the end stage of the disease.[2,6]

Diagnosis
Diagnosing achalasia can be challenging, and patients often experience symptoms for years before obtaining a diagnosis.[9] An important initial step is distinguishing esophageal from oropharyngeal dysphagia through a careful history and evaluation of swallowing by observing the patient drink water. In cases of suspected esophageal dysphagia, structural mechanical obstruction should be ruled out first via upper gastrointestinal endoscopy or radiologic imaging. Endoscopic features supportive of achalasia include a dilated or tortuous esophagus, bolus impactions with or without fluid pooling in the esophagus, and resistance to intubation of the esophagogastric junction (EGJ).[2,5] Esophageal inflammatory changes or ulcerations secondary to stasis, pill esophagitis, or Candida esophagitis can also be seen on endoscopy.[5] To minimize aspiration, patients should restrict oral intake for a minimum of 8 hours prior to endoscopy; in addition, many centers recommend a liquid diet for 48 hours and a soft diet the week prior to endoscopy in cases of suspected achalasia to help clear the contents of the esophagus. During endoscopy, vigorous suctioning of retained fluid in the esophagus should be performed upon entry of the scope. The classic "bird's beak" appearance, of the distal esophagus, a dilated contrast-filled esophagus, "corkscrew" or "rosary bead" appearance and absent peristalsis can be seen on barium esophagram.[2,6] While often nondiagnostic, barium esophagram is particularly helpful in cases with equivocal esophageal manometry

An important initial step is distinguishing esophageal from oropharyngeal dysphagia through a careful history and evaluation of swallowing by observing the patient drink water.

Table 1 CLASSIFICATION OF ESOPHAGEAL MOTILITY DISORDERS WITH IMPAIRED EGJ RELAXATION

Phenotype according to Chicago classification	Features on manometry	Conceptual model of natural history	Considerations
Achalasia, Type I	• 100% absent peristalsis • No significant esophageal pressurization	• Late-stage • Complete loss of inhibitory neurons	• Severe dilation is associated with poor treatment response
Achalasia, Type II	• 100% absent peristalsis • ≥20% of swallows with panesophageal pressurization to > 30 mmHg	• Progressive loss of inhibitory neurons	• Best treatment response
Achalasia, Type III	• ≥20% of swallows with premature spastic contractions (distal latency < 4.5 s)	• May represent a distinct entity unrelated to loss of inhibitory neurons	• Worst treatment response • May benefit from management directed at spasm
Functional EGJ Outflow Obstruction	• Normal or impaired peristalsis	• Early-stage • Variable loss of excitatory and inhibitory influence	• Rule out mechanical obstruction with EUS/CT

Esophagogastric junction, EGJ; Endoscopic ultrasound, EUS; Computerized tomography, CT.

findings and to assess for late-stage achalasia changes that have treatment implications.[5]

Esophageal manometry is the gold standard for diagnosing and classifying achalasia; all patients with suspected achalasia who do not have evidence of a mechanical obstruction should undergo esophageal motility testing.[5] The landmark development of esophageal pressure topography (EPT) in the 1990s has transformed esophageal manometry and the modern approach to achalasia.[11-16] The integrated relaxation pressure (IRP), calculated as the mean of 4 seconds of maximal EGJ relaxation following pharyngeal contraction, is a metric to quantify deglutitive EGJ relaxation and has been instrumental in establishing diagnostic criteria for achalasia.[17-19] While a defined diagnostic threshold continues to be debated, a median IRP greater than 15 mm Hg is concerning for an EGJ outflow disorder. In addition, a classification scheme of esophageal motility disorders utilizing EPT metrics (the Chicago classification) has refined the conventional diagnosis of classic achalasia into three clinically relevant phenotypes (achalasia types I, II, and III); these phenotypes portend prognostic and therapeutic implications, and support the natural history of achalasia (Table 1).[17-20]

Type II achalasia, associated with impaired LES relaxation and pan-esophageal pressurization, results from a progressive loss of inhibitory neurons. Complete loss of contractile activity in the esophageal body is seen in type I achalasia and is considered to represent a later stage of disease progression.[2,20] Cases of impaired LES relaxation with normal or impaired peristalsis are referred to as EGJ outflow obstruction (EGJ-OO), and this may represent an early or incomplete variant of achalasia resulting from a variable loss of excitatory and inhibitory influence. Considered to be a distinct entity, type III achalasia is associated with premature simultaneous contractions and does not follow the typical presentation of progressive neuron loss (Figure 1).[20]

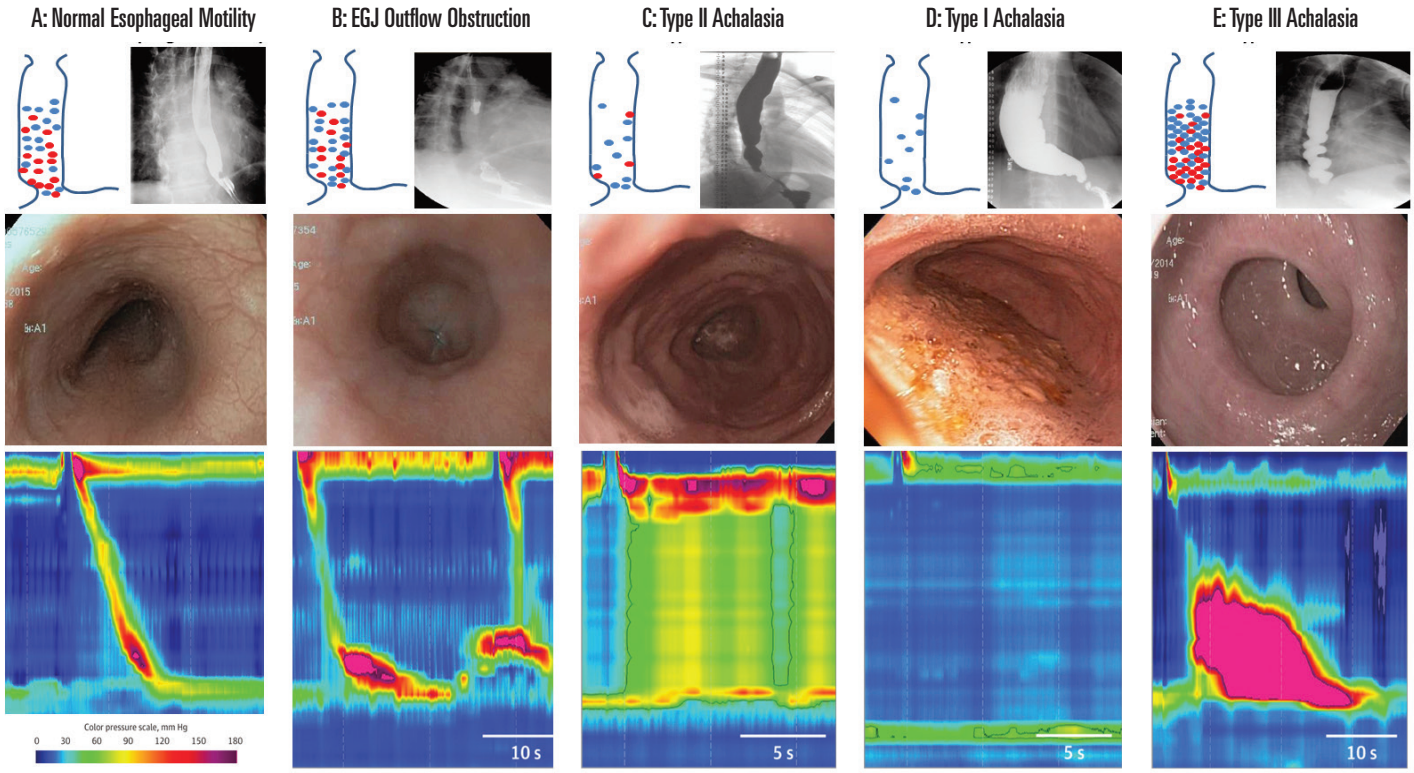
In cases of suspected achalasia, it is imperative to evaluate for pseudoachalasia from infiltrative tumors or secondary achalasia from extrinsic processes such as a tight fundoplication or laparoscopic adjustable gastric banding.[5] Endoscopy with careful evaluation of the gastric cardia in retroflexion and/or barium esophagram is required; and when the suspicion of pseudoachalasia is high, endoscopic ultrasound and/or computerized tomography is recommended.[6] Additionally, achalasia should be considered in patients with refractory reflux, particularly prior to antireflux surgery, as heartburn and regurgitation can be the only presenting symptoms of achalasia; in these patients, esophageal manometry should be performed (Figure 2).[9,10]

Treatment

Curative therapies for achalasia do not exist. The primary management goals hinge on early diagnosis and treatment in order to relieve symptoms, improve esophageal emptying, and prevent late complications. First-line definitive therapies include en-

Achalasia should be considered in patients with refractory reflux, particularly prior to antireflux surgery.

Figure 1



Courtesy Dr. Rena Yadlapati

Achalasia phenotype represented by neuron density, esophagram, endoscopy, and manometry findings. ***A:*** *Normal esophageal motility with intact lower esophageal sphincter (LES) relaxation and propagating contractions. Here there is a gradient distribution of excitatory (blue circles) and inhibitory (red circle) influence in the distal esophagus.* ***B:*** *Esophagogastric junction outflow obstruction pattern with impaired LES relaxation with evidence of propagating contractions. This may represent the point where there is variable loss of excitatory and inhibitory influence in the distal esophagus.* ***C:*** *With progressive loss of inhibitory neurons, the manometric pattern may progress to a type II achalasia with impaired LES relaxation and panesophageal pressurization.* ***D:*** *Type I achalasia likely represents a later phase of disease progression with complete loss of contractile activity in the body of the esophagus and signs of esophageal dilation on esophagram and esophagitis on endoscopy.* ***E:*** *Type III achalasia is associated with premature simultaneous contractions as represented by the corkscrew appearance on esophagram, and may represent an entity distinct from the typical presentation of progressive neuron loss. Barium esophagrams, endoscopic images, and esophageal pressure topography plots reproduced with permission from the Esophageal Center at Northwestern Medicine.*

doscopic approaches with pneumatic dilation and peroral endoscopic myotomy (POEM) or surgery with a Heller myotomy, and should be considered in patients that are good surgical candidates (Table 2).

To perform a pneumatic dilation, a noncompliant cylindrical balloon is fluoroscopically positioned and inflated across the LES. A recommended initial approach is dilation with a 30-mm balloon and, if symptoms persist, to follow with a graded dilation approach as clinically indicated.[6] Pneumatic dilation, as the initial treatment of achalasia, has a reported efficacy of 62%-90%.[6] The risk of perforation from pneumatic dilation ranges from 0% to 16% and is less than 1% when performed by an experienced physician.[6,21]

The preferred approach for surgical myotomy is a laparoscopic Heller myotomy, which surgically divides the circular muscle fibers of the LES with a partial 180° (Dor) to 270° (Toupet) antireflux repair.[22] Laparoscopic Heller myotomy has reported efficacy rates of 88%-95% and is superior to a single pneumatic dilation; however, its superiority is less clear when compared with a graded approach to pneumatic dilation.[23]

POEM, the newest treatment for achalasia, requires creating a submucosal tunnel from the midesophagus to the gastric cardia and performing a selective electrosurgical myotomy of the circular muscle for a minimum length

Table 2

MANAGEMENT OPTIONS FOR ACHALASIA

Patients	Treatment strategy	Procedure description	Procedure setting	Outcomes	Procedural issues
Good Surgical Candidates	Pneumatic Dilation	Fluoroscopic balloon dilation across the LES with noncompliant, cylindrical balloon Recommended: Initially perform 30-mm balloon dilation, followed with a graded approach as indicated	Endoscopy laboratory with fluoroscopy; Moderate sedation/-MAC; Procedure time 30 mins; Observation time 4-6h	62%-90% efficacy; 2-5 years durability (Increased efficacy & durability with graded approach)	0 -16% perforation risk; Does not influence response to subsequent myotomy
	Surgical Myotomy	Typically laparoscopic Heller myotomy with an antireflux repair	OR; General anesthesia; Procedure time 90 mins: Hospital stay 1-2d	88%-95% efficacy; 5-10 year durability	Risk of post-surgical reflux or dysphagia (dependent on surgical approach)
	Peroral Endoscopic Myotomy (POEM)	Creation of an endoscopic submucosal tunnel from mid-esophagus to gastric cardia with selective myotomy	OR; endoscopy laboratory; General anesthesia; Procedure time 90 mins; Overnight observation	Initial success rates > 90%; long-term efficacy unknown	Post-procedural complications and issues unknown
Poor Surgical Candidates Or Unwilling To Have Surgery	Oral Medical Therapy	Nifedipine SL 10-30mg 30-45 mins before meal, Isosorbide dinitrate SL 5-10mg 15 mins before meal, Sildenafil 25-50mg with each meal	N/A	Short-acting temporizing effects	Often have limiting side effects
	Botulinum Toxin	100 units of Botulinum toxin injected 1 cm proximal to SCJ in 4 radially dispersed aliquots with sclerotherapy needle during endoscopy	Endoscopy laboratory; Moderate sedation/-MAC; Procedure time < 30 mins; Observation time 60 mins	Up to 66% effective for up to 6 months; often require repeat injections within 12 months	Overall safe; Repeated injections make subsequent myotomy challenging

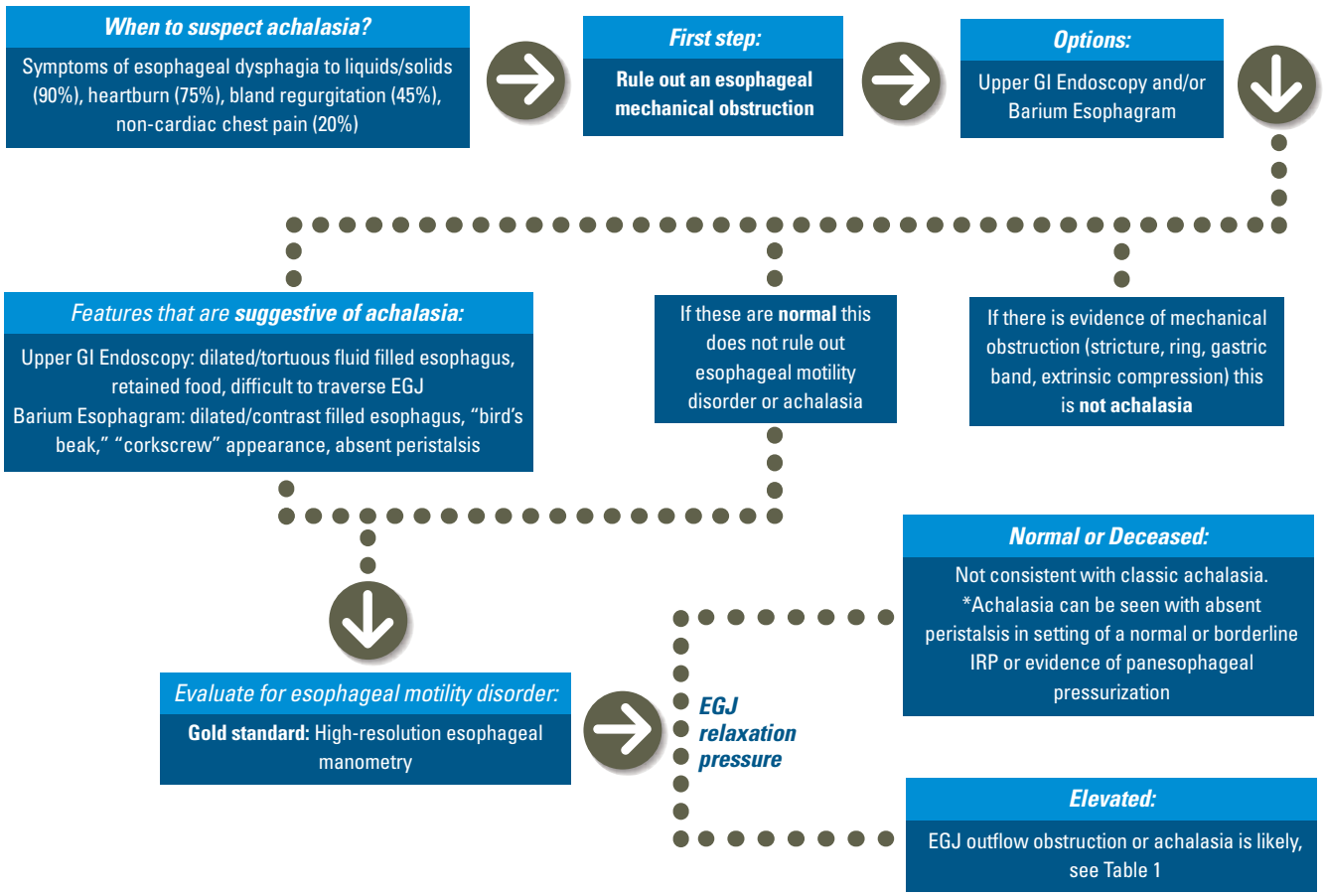
Lower esophageal sphincter, LES; monitored anesthesia care, MAC; operating room, OR; squamocolumnar junction, SCJ

of 6 cm up the esophagus and 2 cm distal to the squamocolumnar junction onto the gastric cardia.[24] Initial success rates of POEM in prospective cohorts of patients with achalasia have been greater than 90%.[24-26] There have been no randomized trials comparing POEM to laparoscopic myotomy or pneumatic dilation and its long-term efficacy remains to be established.

Medical therapy and botulinum toxin should be reserved for patients who are poor candidates for definitive treatment. Calcium channel blockers and oral nitrates may be useful as short-acting temporizing treatments, given their prompt reduction of LES pressure but are poor long-term treatment options due to their limiting adverse effects and inability to prevent disease progression.[27] For patients intolerant or nonresponsive to these agents, sildenafil is an alternative option; however, long-term data examining outcomes and safety are lacking.[28]

Botulinum toxin injection into the LES muscle is a treatment option for achalasia based on its ability to block acetylcholine release. Because of the temporary effect of botulinum toxin, it has limited efficacy beyond 12 months of administration with a high rate of relapse requiring retreatment. Repeated botulinum toxin treatments can make subsequent Heller myotomy more challenging and this should

Figure 2 INITIAL WORK-UP OF SUSPECTED CASES OF ACHALASIA



be considered in the long-term planning of management strategies.[29,30]

Esophagectomy remains a management option for patients with end-stage achalasia who are unresponsive to therapy and are good surgical candidates.[5] The role of EGJ stents as an alternative or complementary management method has been explored and a recent study reported excellent long-term results using a large-diameter partially covered self-expandable metal stent.[31,32]

Follow-up

The optimal follow-up approach for achalasia is focused on periodic evaluation of symptoms, esophageal emptying, and nutrition status. All patients should have a postprocedure evaluation within 3 months after intervention to assess for response. Symptom response is typically gauged by a simple scoring system (the Eckardt score), which grades four symptoms of achalasia: dysphagia, regurgitation, retrosternal pain, and weight loss. Physiologic response can be assessed with timed barium esophagram and/or esophageal manometry and both have been shown to provide valuable prognostic information.[2,6] Although the risk of squamous cell carcinoma is higher in patients with achalasia than in the general population, there are no clear data to support more frequent endoscopic surveillance and this is left to the judgment of the individual physician.[5]

Future work

Over the past 20 years the physiologic mechanisms of achalasia have been better defined and novel treatment strategies to relieve LES pressure have emerged, offering increased palliative options and improved outcomes for patients. However, the etiology of achalasia remains poorly understood and continues to limit early diagnosis and curative interventions. Future work to delineate genetic susceptibilities and autoimmune factors related to achalasia are needed in order to guide the path for therapies that can restore esophageal function. As such, there is ongoing interest in examining the role of neural progenitor cell transplantation to regenerate ganglia.[33] In addition, research is underway to fur-

ther characterize the profile of autoantibodies implicated with achalasia. To date, studies support an organ-specific autoimmune process with cytotoxic T cells as possibly the principal effectors of myenteric degeneration; future research exploring the role of immunomodulator therapies in the management of achalasia is of interest.[7]

Continued investigation into the physiologic nuances of the spectrum of achalasia in order to facilitate earlier detection and intervention is imperative. For instance, the functional lumen imaging probe (FLIP) is a novel diagnostic tool that measures EGJ distensibility and recent studies have demonstrated that intraprocedural EGJ distensibility measurements with FLIP are predictive of postoperative symptomatic outcomes.[34] FLIP provides uniquely valuable information about esophageal compliance and its role as a predictive and prognostic tool for achalasia is an area of ongoing research.[34]

Finally, future work is needed to streamline personalized high-quality patient-centered approaches for achalasia. As such, randomized controlled trials comparing the long-term efficacy, cost-effectiveness, and patient-centered outcomes of current and future treatment strategies should be a research priority. ■

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Dr. John E. Pandolfino and Dr. Rena Yadlapati

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Hospital Clinicians Commonly Work While Sick

By Tara Haelle // Frontline Medical News

WHY DO HOSPITAL DOCTORS GO TO WORK SICK?

The vast majority of doctors and other trained medical professionals at a hospital went to work while sick within the past year, even though they realized the risk that decision places on patients, according to a recent study.

In fact, almost 1 in 10 hospital clinicians worked while sick at least five times in the past year, primarily because of staffing concerns or not wanting to let colleagues down, reported Julia Szymczak, Ph.D., and her associates at the Children's Hospital of Philadelphia (JAMA Pediatr. 2015 July 6 [doi: 10.1001/jamapediatrics.2015.0684]).

"A combination of closed- and open-ended questions illustrated that the decision to work while sick was shaped by systems-level and sociocultural factors that interacted to cause our respondents to work while symptomatic, despite recognizing that this choice may put patients and colleagues at risk," the authors wrote.

Of 929 surveys sent out, 538 clinicians completed them, which included 280 of 459 physicians (61%) and 256 of 470 advanced-practice clinicians (54.5%). The advanced-practice clinicians included registered nurses, physician assistants, clinical nurse specialists, registered nurse anesthetists, and certified nurse midwives. Of those who responded, 15.7% worked in intensive care, 13.1% in surgery, 12.5% in general pediatrics, and 44.8% in another pediatric subspecialty.

Although 95.3% of respondents believed working while sick put patients at risk, 83.1% reported having done so at least once in the past year. Further, that proportion included 52% of all respondents who reported coming to work sick twice in the past year and 9.3% who worked while ill at least five times in the past year.

Nearly a third of respondents said they would work even if they had diarrhea (30%), while 16% said they would work with a fever, and 55.6% would work with acute respiratory symptoms, including cough, congestion, rhinorrhea, and sore throat.

But doctors were more likely than oth-

IN THEIR OWN WORDS ▶

Attending physician, pediatric subspecialty: "Our division does not have any systems in place to support physicians calling out sick. So on the occasions where I have called out sick, it was a disaster: Patients were not called to reschedule, phone calls were not forwarded, etc."

Attending physician, emergency department: "There is an unspoken understanding that you probably should be on your deathbed if you are calling in sick. It inconveniences colleagues, is complicated to pay back shifts, and makes me look bad to do so (like I am weak or something). It is much, much less stressful to suck it up and come in sick than call out."

Attending physician, ICU/critical care: "There is no reliable mechanism to have another person cross-cover on short notice. Everyone is busy. If a person is not on service, he/she is usually doing something that is not easily disrupted. I feel extremely guilty about needing someone else to cover me due to an illness." ■

From JAMA Pediatr. 2015 July 6 (doi:10.1001/jamapediatrics.2015.0684). Quotes are from a cross-sectional, anonymous survey administered to 459 attending physicians and 470 advanced-practice clinicians.

er professionals to say they would go to work with these symptoms: 38.9% of doctors would work despite diarrhea, compared with 19.9% of advanced-practice clinicians. Doctors and advanced-practice clinicians would also work with acute respiratory symptoms (60% vs. 50.8%, respectively), a fever only (21.8% vs. 9.8%), and fever and chills with body aches (18.6% vs. 10.9%, all P < .03).

Nearly every respondent (98.7%) said they worked despite being sick because they did not want to let their colleagues down, just as almost all of them worried the hospital would not have enough staff (94.9%) or that they would let their patients down (92.5%).

Doctors were more likely than other professionals to say they would go to work with these symptoms: diarrhea, fever, and acute respiratory symptoms including cough, rhinorrhea, and sore throat.

Smaller majorities of respondents also worked because others also work while sick (65%), worried their colleagues would ostracize them (64%) if they didn't work, were concerned about their patients' continuity of care (63.8%), had unsupportive leadership (56.2%), or believed they could not be easily replaced (52.6%).

Among the 316 respondents who filled in additional reasons, 64.9% said they had a very hard time finding someone to cover their shift, 61.1% described a strong cultural norm to work unless extremely sick, and 57% expressed uncertainty about what is considered "too sick to work."

The Centers for Disease Control and Prevention funded the research. The authors reported no disclosures. ■

WHEN HEALTH CARE WORKERS ARE SICK, FIRST DO NO HARM

For centuries, a guiding principle for health care workers has been *primum non nocere*, or first do no harm. However, health care workers do exactly that when they work with patients while ill themselves with contagious infections. Even common but untreatable infectious like enterovirus and respiratory syncytial virus can prove deadly to immunocompromised patients.

The propensity to work while ill is influenced by cultural trends. In past years, many ill physicians worked even to the point of receiving intravenous fluids while on the job; working while sick was regarded as a badge of courage. Dr. Szymczak and colleagues identified as an issue the absence of an effective sick relief system that has sufficient flexibility to "staff up" during high rates of health care worker illness. Sick relief systems and policies need to be clear regarding when health care workers should stay away from work, how patient coverage will be ensured, and the availability of and access to paid sick leave.

Determining what constitutes being too sick to work is complicated and lacks a sufficient evidence base. Using a system that bases work restrictions on the presence of key symptoms may add clarity and enable health care workers to recognize when they need to stay home.

Creating a safer and more equitable system of sick leave for health care workers requires a culture change in many institutions to decrease the stigma – internal and external – associated with health care worker illness. Identifying solutions to prioritize patient safety must factor in workforce demands and variability in patient census and emphasize flexibility. Strong administrative and physician leadership and creativity are essential to support appropriate sick leave and ensure adequate staffing. Hospital leadership must ensure that the culture supports a paid sick leave policy that is adequate and nonpunitive. ■

These comments are selected from an accompanying editorial (JAMA Pediatr. 2015 July 6 [doi:10.1001/jamapediatrics.2015.0994]), written by Dr. Jeffrey R. Starke of the department of pediatrics at Baylor College of Medicine in Houston, and Dr. Mary Anne Jackson of the division of infectious diseases at Children's Mercy Hospital, University of Missouri–Kansas City. Dr. Starke and Dr. Jackson reported no disclosures.

Postfellowship Pathways: Consider a Career in the Biopharmaceutical Industry

By Douglas S. Levine, M.D., FACG

Dr. Levine was a fellow and faculty member in the division of gastroenterology at the University of Washington School of Medicine, Seattle. He has worked in clinical research, medical affairs, and management roles at AstraZeneca, Ironwood Pharmaceuticals, and Shire, where he is currently Head of Medical Affairs, Gastroenterology, and Internal Medicine (dolevine@shire.com). He is an employee and shareholder of Shire. The opinions expressed in this article are those of Dr. Levine and not those of Shire.

What is your day-to-day life like in the biopharmaceutical industry?
My role is like an academic division head: I create and implement strategies; manage personnel and budgets; engage in research, publications, and training; and report to a department head. I work with colleagues with different specialized industry expertise, in different medical specialties, inside and outside of departments such as Medical Affairs: Research and Development, Commercial, Regulatory, Information Technology, Legal, Compliance, Human Resources, Finance, Program Management, Corporate Communications, and Corporate Development. Our activities align with company goals such as ensuring the safe and appropriate use of products, helping address patients' unmet medical needs, exploring new treatments for research and development, and sponsoring patient and professional education. Leadership and communication drive progress through the creation of plan documents and reports, team meetings, tele- and video conferences, emails, phone calls, and web-based applications. These activities often lead to collaborative engagements with external stakeholders including content matter experts, members of professional societies, patient advocacy groups, other biopharmaceutical companies, and health care professionals at medical scientific congresses.

What do you enjoy most about working in this industry?
In a word – people. It's about patients and the different individuals I work with both in my company and the health care sector more broadly. These relationships enable the growth and accomplishment essential to any career in which one hopes to excel. It is satisfying to achieve expertise in intellectual disciplines and – for a medical subspecialty – to continue to apply it in patient care, research, writing, and consultation. With the need for medical input into multidisciplinary activities that constitute product development and commercialization, I have the opportunity to assist multifunctional and multicultural global teams in actualizing complex projects. Because of this multifaceted engagement, there are myriad opportunities for interdepartmental and international collaboration in addition to interacting with business clients. With time and experience, one can work as manager and leader as well as assume teaching, coaching, and mentoring responsibilities to support the professional growth of colleagues – things I especially enjoy.

What led you to pursue a career in this field?
Early in training, I developed an interest in the potential benefits of

a drug for inflammatory bowel diseases. As an internist who depended on prescribing medications to treat patients, I became enthusiastic about the possible novel uses of drugs and the insights they might provide into disease processes. Next, I joined a team to investigate GI somatic genetic abnormalities as predictors of progression to cancer. This translational research involved collaboration with basic and applied scientists and clinicians, and yielded findings possible only with integrated, multidisciplinary approaches; all of which are intrinsic to the team-based culture of industry. I cared for patients with Crohn's disease and ulcerative colitis, most of whom were refractory to standard therapies. This prompted me to enlist as an investigator in industry-sponsored clinical trials to help create therapeutic innovations and potentially provide benefits to eligible patients. These experiences have led me to recognize and understand the fundamental role of industry in drug development.

What types of industry opportunities are available for gastroenterologists?

Industry roles are available that match both interests and experience. Medical affairs has field roles (e.g., medical science liaison) focused on engaging expert health care professionals as well as headquarters roles to oversee the accuracy of promotional materials, respond to questions from prescribers, and support research and education initiatives pertinent to products and approved treatment indications. Clinical research involves designing trials in different phases of drug development, monitoring studies in progress, and analyzing and reporting results. Pharmacovigilance involves monitoring, assessing, and reporting adverse events with use of drugs in clinical trials or during the postmarketing period. Medical device companies may attract gastroenterologists interested in developing diagnostic and treatment tools such as endoscopic devices. Physicians with basic science training may qualify for bench science roles in early clinical development, nonclinical research, pharmacology, and toxicology. Physicians with business training may qualify for commercial marketing, analytics, operational, health economic roles, or business leadership positions.

Are there opportunities to still see patients?

Many companies permit physicians time for patient care apart from their day-to-day responsibilities and there are policies in place to address limits on service and malpractice coverage. Physicians new to the industry are allowed to continue patient care in order to sustain skills should they choose to return to full-time practice. Some do this to enhance their capabilities in their industry roles, while others view the activity as distracting from company responsibilities. Employees within the industry are aware of the legal and regulatory boundaries between individual patient-physician relationships and company activities that necessitate medical professional tradeoffs. Instead of directly engaging in individual patient care, industry physicians indirectly participate via drug development that can help patients and provide prescription options for clinicians.

When is the best time to look for a job in the biopharmaceutical industry?

There is no one "best time"! Physicians differ in interests, training, experience, goals, and career paths. Companies vary in the types of jobs offered and availability of entry-level positions versus roles for which experience is required. Postfellowship experience in research and clinical practice is favored by many companies but physicians can enter the industry immediately after training as well as at mid- and end of career.

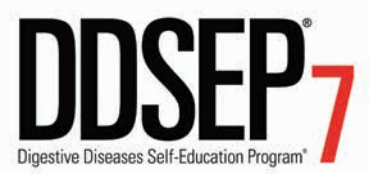
It is more common for applicants to move from academic positions than from clinical practices. Identifying the best time to apply is dependent upon what you learn about the industry and individual companies. Understanding the industry as a whole is important but – as with any job – you should be selective in choosing which companies to target. This research will allow you to find the kinds of opportunities available and help determine the best time to begin your career transition.

What can be done during fellowship/early career to prepare for a career in industry?

During this professional stage, you should focus on current activities in gastroenterology. Your value to any company is a knowledge of GI, special clinical and research topics, investigational methods, clinical skills, and real-world experience. Industry work is team based. Gain experience in working with other physicians, nursing professionals, PhD researchers, and administrators. Capabilities in computer applications may not be essential but basic proficiency will cushion your entry into an industry that relies on digital information management. Learn about industry activities through various organizations such as the American Association of Pharmaceutical Scientists, Biotechnology Industry Organization, and Pharmaceutical Researchers and Manufacturers of America. Seek out industry members who attend medical congresses and talk with faculty at your institution who participate in industry-sponsored trials. Review online listings of com-

panies and investigate websites to learn what products are marketed and/or are in clinical development. Learn about the accomplishments, policies, philosophies, and culture of different companies so you can differentiate them and determine which may be the right fit.

In summary, biopharmaceutical companies provide career opportunities for gastroenterologists that advance patient care and are professionally satisfying. The variety of job roles and large number of companies, which differ in size, scope, and culture, allow for mutually productive matches among physician scientists. If you want to contribute your medical skills to the part of the health care sector that drives creation of drug products to address unmet medical needs, consider a career in the biopharmaceutical industry. ■



ANSWERS // From page 3

Q1: ANSWER: D

CRITIQUE
This patient has no medical comorbidities, and based on epidemiological studies will most likely have a peptic ulcer. He had a bloody NG aspirate, which may limit endoscopic visualization. After stabilization, the first priority is to ensure that timely endoscopy can be performed in an effective manner. The patient has no comorbidities to suggest a variceal bleed, therefore intravenous octreotide (Choice C) and prophylactic antibiotics (Choice E) would be inappropriate. The patient does not demonstrate altered mental status, hemodynamic or respiratory instability, and therefore endotracheal intubation (Choice B) is not necessary. Iced-saline gastric lavage is without demonstrated benefit, and it may be harmful by inducing ischemic mucosal injury to previously noninvolved areas of gastric mucosa (Choice A). Intravenous erythromycin prior to endoscopy has been reported to clear the stomach and improve endoscopic examination. Furthermore, erythromycin was found to be cost effective with an increase in quality-adjusted life-years.

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Q2: ANSWER: D

CRITIQUE
Multiple colorectal adenomas may be attributable to the autosomal dominant polyposis syndrome, familial adenomatous polyposis (FAP), due to germline mutations in the APC gene, or secondary to mutations in the base excision repair gene MUTYH. MUTYH-associated polyposis (MAP) is an autosomal recessive trait characterized by the presence of adenomatous polyposis and an increased risk of colorectal cancer. Germline mutations in MLH1, MSH2, MSH6, PMS2 genes would be indicative of Lynch syndrome. Lynch syndrome is characterized by early onset of CRC and a predisposition to cancers of the endometrium, ovary, stomach, small bowel, urinary tract, and brain. Individuals with Lynch syndrome do not develop a large number of polyps as seen in MAP and FAP. Immunohistochemical analysis and microsatellite instability testing of the sigmoid adenocarcinoma would be indicated if the diagnosis of Lynch syndrome were being considered. BMPR1A, SMAD4 mutations are associated with juvenile polyposis syndrome (JPS) that is characterized by the development of multiple juvenile polyps and not adenomas. STK11 gene mutations are associated with Peutz Jeghers syndrome (PJS). Individuals with PJS do not present with multiple adenomas but instead have hamartomatous polyps.

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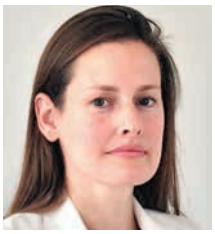
A Personal Story: The Unexpected Benefits of Not Having It All

By Anne Peery, M.D., MSCR



Dr. Peery is an assistant professor of medicine at the University of North Carolina, Chapel Hill.

It felt awkward being asked to write an article on work-life balance for young gastroenterologists. My life is rarely balanced. I owed three papers to the mentor who suggested I take this on. My husband and I were getting ready to move. We had been eating a lot of take-out at home, burritos and burgers, and my 13-month-old son had learned that he really liked French fries. Wordless, he would hold out his hand and ask for them with a grabbing motion. I had been meaning to go to the gym more – doesn't every work-life balance author tell you to make time for exercise? I thought I might need to hire a personal trainer just to get this article written. "I'll do it," I told the editor, "but only if we can push the deadline back to August."

When I started my fellowship in gastroenterology, I barely gave a thought to work-life balance. I wanted all of the research and clinical opportunities I had been offered as well as the people who ran the place to think they had made a good choice by offering those opportunities to me. Even if there were days I might have traded a 2 a.m. food impaction patient for a good night's sleep, or wished for a lighter call schedule, I knew that my fellowship was the right choice for me.

Oddly, the lack of control over my time as a fellow made my years of training easier. I could not change what rotation I was on, or how many patients there would be, or how late the day would go. Outside of clinical decision making, I had only one choice – gastroenterology or something else. I made that choice every day for 4 years. Work-life balance was often about remembering to eat dinner and go to sleep at the end of the day. After I had my first son, it was about letting the baby sleep in bed beside me while I wrote consult notes.

I think most fellows are able to work at this level because we know that training is temporary. People sometimes compare fellowship to a marathon. At the end of a marathon, of course, there is a finish line and you get to stop running. As a trainee, the finish line of fellowship was always clear. After that, the future details of my life could be worked out.

Once I had graduated, however, I found that the work-life balance I promised myself was more challenging than I had imagined. A lot of work-life balance articles offer lists of things to do, and I have made good efforts at many of them. I made time to go the gym. I went out with friends. I scheduled quality time with my family and sometimes I would get a good night's sleep. I investigated different schemes for time management to make sure I was being efficient. I made lists and I stayed organized and I met with my mentors. These were all good things to do but none of these things ever made my life *feel* in balance.

The problem seemed to be that there was always something else of value that I could have been doing instead of what I was actually doing.

Yes, I might be at the gym but should I have been revising a grant application instead? Yes, I was revising a paper for submission but should I have really been spending time with my son who seemed irritable that morning? When I was in training, the few hours under my control offered a limited array of choices. After graduation, I was surrounded with fantastic opportunities but I found myself out of practice at choosing between them. Even worse, I found myself out of practice at accepting the costs and benefits of each choice that I made.

This was a problem that no work-life balance checklist ever solved. Instead, I had to learn to think about things differently. After a decade of doing the clinical and research work assigned to me, I had to relearn to make my own decisions and accept responsibility for those choices.

After 2 years, I am finally succeeding at a different kind of intellectual discipline. If I am with my kids, I know it is important to enjoy that time instead of thinking about the paper I meant to write last week. Even more importantly, if I am tucked into my office and finally writing the paper, I know that I need to accept that my husband and fantastic preschool are taking good care of my kids. I can look at a picture of them and smile (there are lots of these pictures on my computer) but then I need to let myself enjoy writing.

COURTESY DR. ANNE PEERY

Dr. Anne Peery and her two young sons at home.

If I am with my kids, I know it is important to enjoy that time instead of thinking about the paper I meant to write last week.

All of us in medicine are fortunate. We get to do complex, intellectually satisfying work that helps people. I consider myself even more fortunate to have supportive colleagues who value my family and a supportive physician husband who values my career. At the end of the day, however, all the support in the world will not help you feel balanced if you focus on everything you have to do instead of the thing you are actually doing. Taking responsibility for my choices has helped me be more present in every part of my life. It has been the hardest part of becoming an attending but it has given me a much better sense of who I am.

So by all means, make time to exercise. Go out with friends. Meet with your mentors. Everything the other articles tell you may be helpful. But also, be sure to appreciate your life and your career as they are happening. Be sure to accept and embrace the sometimes-difficult decisions you have to make about time management. You will never find some simple trick for getting everything done. After all, it's "everything." Instead, enjoy and commit to the things you take on. In a long and full life in medicine and the world, that will almost assuredly be enough. ■

The Answer

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

This is intestinal transplant–associated microangiopathy (ITAM), a life-threatening complication of allogeneic bone marrow transplantation. Transplant-associated microangiopathy can be systemic (characterized by hemolysis with schistocytes, thrombocytopenia, renal and neurologic dysfunction, and elevated lactate dehydrogenase) or isolated to the intestine.[1] The incidence is unknown, but the condition is likely underrecognized. Risk factors for ITAM are intestinal GVHD, CMV colitis, and treatment with calcineurin inhibitors. Figures A and B show the discrete ulcers scattered along the entire colon and small whitish plaques (thin arrows in Figure A). The latter was a manifestation of pseudolipomatosis (innocuous small air bubbles in the mucosa).

Pathology is shown in Figures C and D. Pathology is the gold standard for diagnosis: Microangiopathy (thick arrows), crypt loss, and platelet thrombi (thin arrows) are present. Apoptotic bodies in the crypts can be seen (vertical arrows in D).

This condition has to be distinguished from GVHD: The therapy offers few good options — intensified immunosuppression/calcineurin inhibitors are discontinued, an approach opposite of the treatment for GVHD.[2]

Recombinant thrombomodulin can be tried. Prognosis is poor as underlined by mortality reported between 30% and 57% of cases.

Tapering of immunosuppression in the patient proved efficacious. He was discharged 6 days later with considerable reduction of volume of stools. ■

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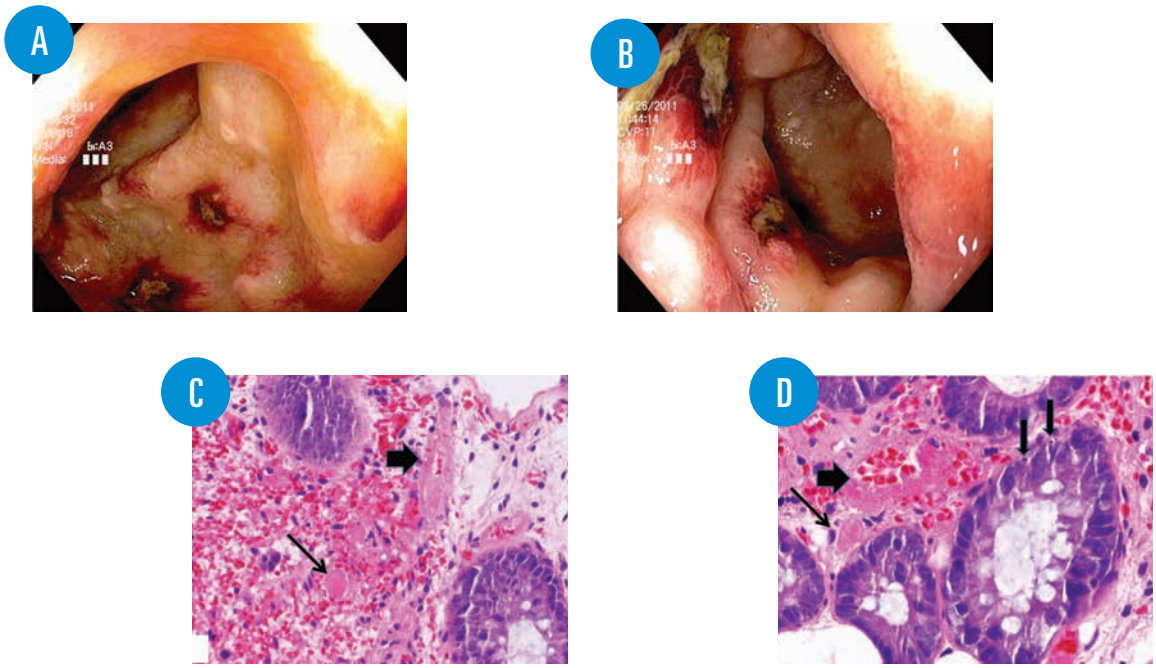

IMPORTANT SAFETY INFORMATION

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.

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