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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

COURTESY DR. COREY A. SIEGEL

Disease severity indexes were created for each severity attribute on a 100-point scale, reported Dr. Corey A. Siegel.

New study establishes IBD severity index

BY MADHU RAJARAMAN
Frontline Medical News

Experts have established a severity index for inflammatory bowel disease (IBD), according to results of an analysis published in the journal Gut (doi: 10.1136/gutjnl-2016-312648).

The index, conceived by a panel of IBD specialists from the International Organization for the Study of Inflammatory Bowel Diseases, is a step toward the standardization of disease severity definitions in ulcerative colitis and Crohn's disease.

The panel determined 16 severity attributes for Crohn's disease and 13 for ulcerative colitis. The analysis found that, in Crohn's disease, mucosal lesions, fistulas, and abscesses were the greatest contributors to disease severity at 15.8%, 10.9%, and 9.7%, respectively. In ulcerative colitis, 18.1% of disease severity was attributed to mucosal lesions, 14% to impact on daily activities, and 11.2% to C-reactive protein, wrote Corey A. Siegel, MD, MS, of the Dartmouth-Hitchcock Medical Center in Lebanon, N.H., and his coauthors.

Investigators used a PubMed literature search to identify three broad elements of disease severity: impact of disease symptoms on daily activities, inflammatory burden, and disease course.

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Incorporating psych care in management of chronic digestive diseases

BY CHHAVI JAIN
Frontline Medical News

Psychogastroenterology is the science of applying psychological principles and techniques to alleviate the burden of chronic digestive diseases. This burden includes digestive symptoms and disease severity, as well as patients' ability to cope with them. Chronic digestive diseases, such as irritable bowel syndrome, gastroesophageal reflux disease, and inflammatory bowel diseases, cannot be disentangled from their psychosocial context. In this regard, the role of gastroenterologists in promoting best practices for the assessment and referral of patients across the spectrum of disease to brain-gut psychotherapies is crucial.

In a review by Laurie Keefer, PhD and her coauthors, published in the April issue of Gastroenterology, provided a clinical update on the structure and efficacy of two major classes of psychogastroenterology – cognitive-behavioral therapy (CBT) and gut-directed hypnotherapy (HYP). The review discussed the effects of these therapies on GI symptoms and the patients' ability to improve coping, resilience, and self-regulation. The review also provided a framework to understand

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NASH rapidly overtaking hepatitis C as cause of liver cancer

BY BIANCA NOGRADY
Frontline Medical News

Nonalcoholic steatohepatitis (NASH) is rapidly eclipsing hepatitis C virus (HCV) infection as the leading contributor to liver cancer in the United States.

Researchers reported on their analysis of past prevalence of HCV, NASH, and alcoholic cirrhosis and prediction of future trends and their effect on hepatocellular carcinoma in the Journal of Clinical and Experimental Hepatology.

The analysis, based on data from the National Health and Nutrition Examination Survey and the Organ Procurement and

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LETTER FROM THE EDITOR: Hope, hepatology, and social determinants of health

Welcome to the April edition of *GI & Hepatology News*. April has always been a month in which we have a sense of renewal and hope. For those of us living in northern climes, both the distinct change in daylight and the melting of the snow (finally) both lift us from the doldrums of winter darkness.


DR. ALLEN

In just over 2 months, we will gather in Washington for Digestive Disease Week.® I have seen a preview of AGA plenary sessions (basic science and clinical). They will be terrific. We will hear about advances in areas such as the microbiome, IBD-related inflammatory pathways, new insights into functional bowel disorders, and a myriad of new therapeutics (both medical and device) for us to share with our patients.

In this month's issue, we touch on themes that will carry into DDW. Substantial work is being done to better define an IBD severity index. These metrics are of critical importance for clinical researchers to use as we investigate the efficacy and effectiveness of new IBD drugs. You can also read about incorporating psychological care in the management of chronic diseases – a topic becoming more important as we expand our focus beyond just the biology of disease and into social determinants of health as we continue our transition to value-based reimbursement. Another topic included this month (and to which several DDW sessions are dedicated) is the devastating impact of opiates on our patients.

We have included a number of hepatology articles this month, such as the front-page story on NASH and its relationship with hepatocellular cancer. Pioglitazone benefits NASH patients with and without type 2 diabetes, and biomarkers may predict liver transplant failures. There are selected articles about Barrett's esophagus progression and risk stratification for colorectal cancer.

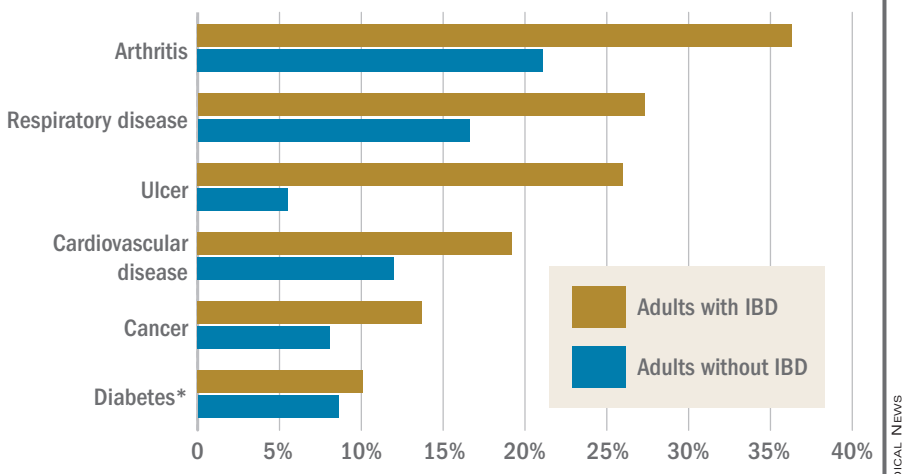
From Washington, we have received some good news. Please see the AGA commentary on the proposed budget. We were reminded recently about how federal politics can impact U.S. medicine. With the (very late) reauthorization of the Children's Health Insurance Plan (CHIP), we saw how political dysfunction can impact millions of American family's lives. Changes in 340-B funding, continued transition from commercial to government payers, a tightening labor market, and relentless increases in overhead expenses, all combine to reduce financial margins of both academic and nonacademic health systems. Economic pressures are leading to massive consolidations within the health care delivery system. Vertical integrations now have supplanted horizontal integrations as the industry trend. This situation will affect many of our independent gastroenterology practices as demand-side management by large national corporations increases.

Economic pressures are leading to massive consolidations within the health care delivery system.

John I. Allen, MD, MBA, AGAF
Editor in Chief

DATA WATCH

Prevalence of chronic conditions by IBD status



*Difference is not significant

Note: Based on data from the National Health Interview Survey, 2015 and 2016.

Source: MMWR. 2018;67(6):190-5

FRONTLINE MEDICAL NEWS

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FRONTLINE MEDICAL COMMUNICATIONS

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References: 1. IMS Health, NPA Weekly, May 2017. **2.** Rex DK, DiPalma 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.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2012. **4.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53.

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FDA issues warning to duodenoscope manufacturers

BY LORI LAUBACH
Frontline Medical News

The Food and Drug Administration issued warning letters to all three duodenoscope manufacturers for failing to comply with the requirements of federal law under which they were ordered to conduct postmarket surveillance studies to assess the effectiveness of reprocessing the devices.

The warning is part of an ongoing effort to prevent patient infections associated with the transmission of bacteria from contaminated duodenoscopes. The three manufacturers – Olympus, Fujifilm, and Pentax – are required to conduct studies to sample and culture reprocessed duodenoscopes that are in clinical use to learn more about issues that contribute to contamination, and to study human factors to determine how hospital staff who have had training are following the reprocessing instructions. In 2015, the FDA ordered the companies to conduct a postmarket surveillance study to determine whether health care facilities were able to properly clean and disinfect the devices.

If the companies fail to respond to the warning letter, the FDA states that they may take additional action, such as seizure, injunction, and civil monetary penalties.

Currently, the Olympus manufacturer has failed to start data collection, while both Pentax and Fujifilm have failed to provide sufficient data required for their respective studies to sample and culture reprocessed duodenoscopes that are in clinical use. In addition, Olympus and Pentax have not complied with requirements to assess how well staff members have followed the reprocessing instructions after the human factors studies and Fujifilm has been meeting its requirements for its human factors study only.

"The FDA has taken important steps to improve the reprocessing of duodenoscopes, and we've seen a reduction in reports of patient infections, but we need the required postmarket studies to determine whether these measures are being properly implemented in real-world clinical settings and whether we need to take additional action to further improve the safety of these devices," said Jeff Shuren, MD, director of the FDA's Center for Devices and Radiological Health in a press release.

The companies had until March 24 to submit a plan that outlines how study milestones will be achieved. If the companies fail to respond to the warning letter, the FDA states that they may take additional action, such as seizure, injunction, and civil monetary penalties.

Read the full press release on the FDA's website.

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Congressional budget includes AGA wins

BY JOHN W. GARRETT, MD, MS, AGAF, AGA PRACTICE COUNCILLOR, MISSION HEALTH, ASHEVILLE, N.C.

AGA spends a lot of time on Capitol Hill advocating to help gastroenterologists in practice better care for their patients and receive fair reimbursement. Therefore, we were pleased that the budget deal passed by Congress and signed by the president in February included several policy victories that AGA has been working diligently on for many years.

IPAB repeal

AGA, and all of organized medicine, have long opposed the Independent Payment Advisory Board (IPAB) that was created as part of the Affordable Care Act. IPAB is an unelected, unaccountable board whose sole purpose is to cut Medicare spending from providers should Medicare reach a certain threshold of spending. Since hospitals are exempt from their purview, physicians would be particularly vulnerable to cuts. However, repealing IPAB has had bipartisan support over the years, and we applaud Congress for listening to us and the medical community and taking action.

Misvalued codes

AGA and the physician community were also successful in removing a provision that would have extended the misvalued codes initiative for the next two years to reallocate savings from potentially overvalued codes. AGA, the Alliance of Specialty Medicine and the AMA opposed the original provision expanding the misvalued codes initiative and have argued that virtually all codes under the fee schedule, including gastroenterology, have been re-evaluated and have already faced significant cuts. In the final agreement, Congress eliminated recapturing savings from the misvalued codes initiative and instead lowered overall updates for physician reimbursement under Medicare by .25 percent for 1 year. Although AGA would prefer this reduction not be included, it is much better than the misvalued codes provision, which disproportionately impacts specialties, like gastroenterology.

DR. GARRETT

Geographic Practice Cost Index

The budget agreement extends the work for the Geographic Practice Cost Index (GPCI) floor for two additional years, which avoids a decrease in Medicare reimbursement for physicians that practice in rural areas. The work GPCI is a variable that Medicare uses to adjust the work component of physician payment based on where they live. A work GPCI floor of 1.0 protects physicians in low-cost, often rural areas, from being paid less for the work they do.

Meaningful use standards

The package addresses electronic health record (EHR) standards and eases requirements for physicians. The language removes the mandate that meaningful use standards become more stringent over time, which is a major financial burden for physician practices. The language also gives physicians more time to submit and receive a hardship exemption from the current EHR standards that would apply to meaningful use and the Quality Payment Program's advancing care information performance category.

Biosimilars coverage under Medicare Part D

The agreement also levels the playing field between biologics and biosimilars by adding biosimilars to the Medicare Coverage Gap Discount Program. Additionally, by providing the 50 percent discount equally, beneficiary out-of-pocket costs will be reduced and the Medicare program will save money as a result of covering the less expensive medication.

AGA and the medical community have fought long and hard for these provisions and are happy to see them finally being implemented. We thank all of our members who have worked along with us to ensure that the voice of gastroenterology continues to be heard on Capitol Hill.

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FROM THE AGA JOURNALS

Bioengineered liver models screen drugs

BY CHHAVI JAIN
Frontline Medical News

Bioengineered liver models have enabled recapitulation of liver architecture with precise control over cellular microenvironments, resulting in stabilized liver functions for several weeks in vitro. Studies have focused on using these models to investigate cell responses to drugs and other stimuli (for example, viruses and cell differentiation cues) to predict clinical outcomes. Gregory H. Underhill, PhD, from the department of bioengineering at the University of Illinois at Urbana-Champaign and Salman R. Khetani, PhD, from the department of bioengineering at the University of Illinois in Chicago presented a comprehensive review of these advances in bioengineered liver models in Cellular and Molecular Gastroenterology and Hepatology (doi: 10.1016/j.jcmgh.2017.11.012).

Drug-induced liver injury is a leading cause of drug attrition in the United States, with some marketed drugs causing cell necrosis, hepatitis, cholestasis, or fibrosis. Although the Food and Drug Administration requires preclinical drug testing in animal models, differences in species-specific drug metabolism and human genetics may result in inadequate identification of potential for human drug-induced liver injury. Some bioengineered liver models for in vitro studies are based on tissue engineering using high-throughput microarrays, protein micropatterning, microfluidics, specialized plates, biomaterial scaffolds, and bioprinting.

High-throughput cell microarrays enable systematic analysis of a large number of drugs or compounds at a relatively low cost. Several culture platforms have been developed using multiple sources of liver cells, including cancerous and immortalized cell lines. These platforms show enhanced capabilities to evaluate combinatorial effects of multiple signals with independent control of biochemical and biomechanical cues. For instance, a microchip platform for transducing 3-D liver cell cultures with genes for drug metabolism enzymes featuring 532 reaction vessels (micropillars and corresponding microwells) was able to provide information about certain enzyme combinations that led to drug toxicity in cells. The high-throughput cell microarrays are, however, primarily dependent on imaging-based readouts and have a limited ability to investigate cell responses to gradients of microenvironmental signals.

Liver development, physiology, and pathophysiology are dependent on homotypic and heterotypic interactions between parenchymal and nonparenchymal cells (NPCs). Cocultures with both liver- and nonliver-derived NPC types, in vitro, can induce liver functions transiently and have proven useful for investigating host responses to sepsis, mutagenesis, xenobiotic metabolism and toxicity, response to oxidative stress, lipid metabolism, and induction of the acute-phase response. Micropatterned cocultures (MPCCs) are designed to allow the use of different NPC types without significantly altering hepatocyte homotypic interactions. Cell-cell interactions can be precisely controlled to allow for stable functions for up to 4-6 weeks, whereas more randomly distributed cocultures have limited stability. Unlike randomly distributed cocultures, MPCCs can be infected with HBV, HCV, and malaria.

Randomly distributed spheroids or organoids enable 3-D establishment of homotypic cell-cell interactions surrounded by an extracellular matrix. The spheroids can be further cocultured with NPCs that facilitate heterotypic cell-cell interactions and allow the evaluation of outcomes resulting from drugs and other stimuli. Hepatic spheroids maintain major liver functions for several weeks and have proven to be compatible with multiple applications within the drug development pipeline.

These spheroids showed greater sensitivity in identifying known hepatotoxic drugs than did short-term primary human hepatocyte (PHH) monolayers. PHHs secreted liver proteins, such as albumin, transferrin, and fibrinogen, and showed cytochrome-P450 activities for 77-90 days when cultured on a nylon scaffold containing a mixture of liver NPCs and PHHs.

Potential limitations of randomly distributed spheroids include necrosis of cells in the center of larger spheroids and the requirement for expensive confocal microscopy for high-content imaging of entire spheroid cultures. To overcome the limitation of disorganized cell-type interactions over time within the randomly distributed spheroids/organoids, bioprinted human liver organoids are designed to allow precise control of cell placement.

Another bioengineered liver model is based on perfusion systems or bioreactors that enable dynamic fluid flow for nutrient and waste exchange. These so called liver-on-a-chip devices contain hepatocyte aggregates adhered to collagen-coated microchannel walls; these are then perfused at optimal flow rates both to meet the oxygen demands of the hepatocytes and deliver a low shear stress to the cells that's similar to what would be the case in vivo. Layered architectures can be created with single-chamber or multichamber, microfluidic device designs that can sustain cell functionality for 2-4 weeks.

Some of the limitations of perfusion systems include the potential binding of drugs to tubing and other materials used, large dead volume requiring higher quantities of novel compounds for the treatment of cell cultures, low throughput, and washing away of built-up beneficial molecules with perfusion.

The ongoing development of more sophisticated engineering tools for manipulating cells in culture will lead to advances in bioengineered livers that will show improving sensitivity for the prediction of clinically relevant drug and disease outcomes.

This work was funded by National Institutes of Health grants. Dr. Khetani disclosed a conflict of interest with Ascendance Biotechnology, which has licensed the micropatterned coculture and related systems from Massachusetts Institute of Technology, Cambridge, and Colorado State University, Fort Collins, for commercial distribution. Dr. Underhill disclosed no conflicts.

ginews@gastro.org

SOURCE: Underhill GH and Khetani SR. Cell Molec Gastro Hepatol. 2017. doi: org/10.1016/j.jcmgh.2017.11.012.

Thirty to 50 new drugs are approved in the United States annually, which costs approximately $2.5 billion/drug in drug development costs. Nine out of 10 drugs never make it to market, and of those that do, adverse events affect their longevity. Hepatotoxicity is the most frequent adverse drug reaction, and drug-induced liver injury, which can lead to acute liver failure, occurs in a subset of affected patients. Understanding a drug's risk of hepatotoxicity before patients start using it can not only save lives but also conceivably reduce the costs incurred by pharmaceutical companies, which are passed on to consumers.


DR. CARR

In Cellular and Molecular Gastroenterology and Hepatology, Underhill and Khetani summarize available and emerging cell-based, high-throughput systems that can be used to predict hepatotoxicity. These modalities include cellular microarrays of single cells, cocultures of liver parenchymal and nonparenchymal cells, organoids (3-D organ-like structures), and liver-on-a-chip devices (complex perfusion bioreactors that allow for modulation of the cellular microenvironment). These in vitro systems have not only enabled investigators to screen multiple drugs at the same time but also have informed the clinical translation of these technologies. For example, the extracorporeal liver assist device – essentially, a liver bypass – and similar bioartificial liver devices can in principal temporarily perform some of the major liver functions while a patient's native liver heals from drug-induced liver injury or other hepatic injury.

However, just as we have seen with the limitations of the in vitro systems, bioartificial livers are unlikely to be successful unless they integrate the liver's complex functions of protein synthesis, immune surveillance, energy homeostasis, and nutrient sensing. The future is bright, though, as biomedical scientists and bioengineers continue to push the envelope by advancing both in vitro and bioartificial technologies.

Rotonya Carr, MD, is an assistant professor of medicine in the division of gastroenterology at the University of Pennsylvania, Philadelphia. She receives research support from Intercept Pharmaceuticals.

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Reference: 1. Clinical decision support tools. American Gastroenterological Association website. http://campaigns.gastro.org/algorithms/constipation/index.html. Accessed May 12, 2017.

FROM THE AGA JOURNALS

Pioglitazone benefited NASH patients with/without t2d

BY AMY KARON
Frontline Medical News

Pioglitazone therapy given for 18 months benefited patients with nonalcoholic steatohepatitis (NASH) similarly, regardless of whether they had diabetes or prediabetes, according to the results of a randomized prospective trial.

The primary outcome, at least a 2-point reduction in nonalcoholic fatty liver disease activity score, compared with placebo, without worsening fibrosis, was met by 48% of NASH patients with type 2 diabetes and by 46% of those with prediabetes, reported Fernando Bril, MD, of the division of endocrinology, diabetes, and metabolism at the University of Florida, Gainesville, and his associates. The report was published in the April issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.12.001).

NASH resolved completely in 44% with type 2 diabetes and 26% of patients without it, perhaps indicating that pioglitazone acts slightly differently when patients with NASH have type 2 diabetes, according to the investigators. "Although the effects on fibrosis appear to be similar in both groups, pioglitazone may contribute to halting [its] rapid progression [in type 2 diabetes]," they wrote. "These differences will deserve further exploration in larger clinical trials."

The trial (NCT00994682) enrolled 101 patients with biopsy-confirmed NASH, of whom 52 had type 2 diabetes and 49 had prediabetes based on clinical history, baseline fasting plasma glucose, hemoglobin A_{1c}, and an oral glucose tolerance test, as per American Diabetes Association guidelines. After a 4-week run-in period, patients were randomly assigned to receive either pioglitazone (45 mg per day) or placebo for 18 months. All patients received lifestyle counseling and a hypocaloric (500-kcal reduced) diet.

Compared with placebo, pioglitazone improved most secondary outcomes similarly regardless of whether patients had type 2 diabetes or prediabetes. The two exceptions were fibrosis and insulin sensitivity of adipose tissue. Patients with type 2 diabetes only experienced improved fibrosis in the setting of pioglitazone therapy (P = .035 vs. baseline). In prediabetic patients, fibrosis lessened moderately over time, regardless of whether they received pioglitazone or placebo. Insulin sensitivity of adipose tissue improved much more markedly with treatment in patients with type 2 diabetes (P less than .001 vs. baseline) than in those with prediabetes (P = .002 for type 2 diabetes vs. prediabetes).

Compared with placebo, pioglitazone improved hepatic and skeletal muscle insulin sensitivity similarly, regardless of diabetes status. Likewise, intrahepatic triglyceride content, as measured by proton magnetic resonance spectroscopy, fell by 11% in pioglitazone recipients with type 2 diabetes and by 9% in those with prediabetes, a nonsignificant difference. Pioglitazone also led to a statistically similar decrease in plasma alanine aminotransferase level regardless of whether patients had type 2 diabetes (50 U/L) or were prediabetic (36 U/L).

Compared with placebo, pioglitazone improved most secondary outcomes similarly regardless of whether patients had type 2 diabetes or prediabetes. The two exceptions were fibrosis and insulin sensitivity of adipose tissue.

This trial's key takeaway is that pioglitazone improves liver histology in NASH whether or not patients are diabetic, said the researchers. "We believed that it was essential to compare its efficacy in patients with [and] without [type 2 diabetes] because of the vast number of patients with prediabetes and NASH and given the significant metabolic and cardioprotective effects of pioglitazone among patients without type 2 diabetes," they wrote. The natural history of NASH is worse in the presence of type 2 diabetes, which might explain pioglitazone's superior effects on fibrosis and insulin sensitivity of adipose tissue in this population, they added.

The Burroughs Wellcome Fund, the American Diabetes Association, and the Veteran's Affairs Merit Award supported the work. Senior author Kenneth Cusi, MD, disclosed nonfinancial support from Takeda Pharmaceuticals, grants from Novartis and Janssen Research and Development, and consulting relationships with Eli Lilly, Tobira Therapeutics, and Pfizer. The other authors had no conflicts.

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SOURCE: Bril F et al. Clin Gastroenterol Hepatol. 2018 Feb 24. doi: 10.1016/j.cgh.2017.12.001.

Biomarker predicted primary nonfunction after transplant

BY AMY KARON
Frontline Medical News

Increased donor liver perfusate levels of an underglycosylated glycoprotein predicted primary transplant nonfunction with 100% accuracy in two prospective cohorts, researchers reported in Gastroenterology.

Glycomic alterations of immunoglobulin G "represent inflammatory disturbances in the liver that [mean it] will fail after transplantation," wrote Xavier Verhelst, MD, of Ghent (Belgium) University Hospital and his associates. The new glycomarker "could be a tool to safely select high-risk organs for liver transplantation that otherwise would be discarded from the donor pool based on a conventional clinical assessment" and also could help prevent engraftment failures. "To our knowledge, not a single biomarker has demonstrated the same accuracy today," they wrote in the April issue of Gastroenterology.

Chronic shortages of donor livers contribute to morbidity and death worldwide. However, relaxing donor criteria is controversial because of the increased risk of primary nonfunction, which affects some 2%-10% of liver transplantation patients, and early allograft dysfunction, which is even more common. Although no reliable scoring systems or biomarkers have been able to predict these outcomes prior to transplantation, clinical glycomics of serum has proven useful for diagnosing hepatic fibrosis, cirrhosis, and hepatocellular carcinoma and for distinguishing hepatic steatosis from nonalcoholic steatohepatitis.

"Perfusate biomarkers are an attractive alternative [to] liver biopsy or serum markers, because perfusate is believed to represent the condition of the entire liver parenchyma and is easy to collect in large volumes," the researchers wrote.

Accordingly, they studied 66 patients who underwent liver transplantation at a single center in Belgium and a separate validation cohort of 56 transplantation recipients from two centers. The most common reason for liver transplantation was decompensated cirrhosis secondary to alcoholism, followed by chronic hepatitis C or B virus infection, acute liver failure, and polycystic liver disease.

Donor grafts were transported using cold static storage (21° C), and hepatic veins were flushed to collect perfusate before transplantation. Protein-linked N-glycans were isolated from these perfusate samples and analyzed with a multicapillary electrophoresis-based ABI3130 sequencer.

The four patients in the primary study cohort who developed primary nonfunction resembled the others in terms of all clinical and demographic parameters ex-

Continued on following page

FROM THE AGA JOURNALS

Opioids linked to mortality in inflammatory bowel disease

BY AMY KARON
Frontline Medical News

Among patients with inflammatory bowel disease (IBD), opioid prescriptions tripled during a recent 20-year period, and heavy use of strong opioids was a significant predictor of all-cause mortality, according to a large cohort study reported in the April issue of Clinical Gastroenterology and Hepatology.

Because this study was retrospective, it could not establish causality, said Nicholas E. Burr, MD, of the University of Leeds (England) and his associates. But "[de]signing and conducting a large-scale randomized controlled trial may not be feasible," they wrote. "Despite the limitations of observational data, population data sets may be the best method to investigate a potential effect."

The gastrointestinal side effects of many analgesics complicate pain management for patients with IBD, who not only live with chronic abdominal pain but also can develop arthropathy-related musculoskeletal pain, chronic widespread pain, and fibromyalgia. In addition to the risk of narcotic bowel syndrome associated with opioid use in IBD, opioids can mask flares in IBD or can cause toxic dilatation if administered during acute flares, the researchers noted. Because few studies had examined opioid use in IBD, the investigators retrospectively studied 3,517 individuals with Crohn's disease and 5,349 patients with ulcerative colitis from ResearchOne, a primary care electronic health records database that covers about 10% of patients in England. The data set excluded patients with indeterminate colitis or who underwent colectomy for ulcerative colitis.


LIDERINA/THINKSTOCK

From 1990 through 1993, only 10% of patients with IBD were prescribed opioids, compared with 30% from 2010 through 2013 (*P* less than .005). After the investigators controlled for numerous demographic and clinical variables, being prescribed a strong opioid (morphine, oxycodone, fentanyl, buprenorphine, methadone, hydromorphone, or pethidine) more than three times per year significantly correlated with all-cause mortality in both Crohn's disease (hazard ratio, 2.2; 95% confidence interval, 1.2-4.0) and ulcerative colitis (HR, 3.3; 95% CI, 1.8-6.2), the researchers reported.

Among patients with ulcerative colitis, more moderate use of strong opioids (one to three prescriptions annually) also significantly correlated with all-cause mortality (HR, 2.4; 95% CI, 1.2-5.2), as did heavy use of codeine (HR, 1.8; 95% CI, 1.1-3.1), but these associations did not reach statistical significance among patients with Crohn's disease. Tramadol was not linked to mortality in either IBD subtype when used alone or in combination with codeine.

Dr. Burr and his associates said they could not control for several important potential confounders, including fistulating disease, quality of life, mental illness, substance abuse, and history of abuse, all of which have been linked to opioid use in IBD. Nonetheless, they found dose-dependent correlations with mortality that highlight a need for pharmacovigilance of opioids in IBD, particularly given dramatic increases in prescriptions, they said. These were primary care data, which tend to accurately reflect long-term medication use, they noted.

Crohn's and Colitis U.K. and the Leeds Teaching Hospitals NHS Trust Charitable Foundation provided funding. The investigators reported having no conflicts of interest.

ginews@gastro.org

SOURCE: Burr NE et al. Clin Gastroenterol Hepatol. 2017. doi: 10.1016/j.cgh.2017.10.022.

Balancing control of pain and prevention of opioid-related morbidity and mortality remains a major challenge for health care providers, particularly in IBD. This study by Burr et al. highlights the potential dangers of opiate use among patients with IBD with the finding that opioid prescriptions at least three times per year were associated with a two- to threefold increase in mortality. Another important observation from this study was that the prevalence of opioid use among IBD patients increased from 10% to 30% during 1990-2013. One would like to believe that, with better treatment modalities for IBD, fewer patients would require chronic opioid medications over time; however, this observation suggests that there has been a shift in the perception and acceptance of opioids for IBD patients.


DR. HOU

Studying opioid use among IBD patients remains challenging as even well-controlled retrospective studies are unable to fully separate whether opioid use is merely associated with more aggressive IBD courses and hence worse outcomes or whether opioid use directly results in increased mortality. As clinicians, we are left with the difficult balance of addressing true symptoms of pain with the potential harm from opioids; we often counsel against the use of nonsteroidal anti-inflammatory medications in IBD, and yet there is growing concern about use of opioids in this same population.

Further research is needed to address patients with pain not directly tied to inflammation or complications of IBD, as well as nonmedical, behavioral approaches to pain management.

Jason K. Hou, MD, MS, is an investigator in the clinical epidemiology and outcomes program, Center for Innovations in Quality, Effectiveness and Safety at the Michael E. DeBakey VA Medical Center, Houston; an assistant professor, department of medicine, section of gastroenterology & hepatology, Baylor College of Medicine, Houston; and a codirector of Inflammatory Bowel Disease Center at the VA Medical Center at Baylor. He has no conflicts.

Continued from previous page

cept that they had a markedly increased concentration (*P* less than .0001) of a single-glycan, agalacto core-alpha-1,6-fucosylated biantennary glycan, dubbed NGA2F.

The single patient in the validation cohort who developed primary nonfunction also had a significantly increased concentration of NGA2F (*P* = .037). There were no false positives in either cohort, and a 13% cutoff for perfusate NGA2F level identified primary nonfunction with 100% accuracy, the researchers said. In a multivariable model of donor risk index and perfusate markers, only NGA2F was prognostic for developing primary nonfunction (*P* less than .0001).

The researchers found no specific glycomic signature for early allograft dysfunction, perhaps because it is more complex and multifactorial, they wrote. Although electrophoresis testing took 48 hours, work is underway to shorten this to a "clinically acceptable time frame," they added. They recommended multicenter studies to validate their findings.

Organizations that provided funding included the Research Fund – Flanders and Ghent University. The researchers reported having no conflicts of interest.

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SOURCE: Verhelst X et al. Gastroenterology. 2018 Jan 6. doi: 10.1053/j.gastro.2017.12.027.

FROM THE AGA JOURNALS

Model predicted Barrett's esophagus progression

BY AMY KARON
Frontline Medical News

A scoring model encompassing just four traits accurately predicted which patients with Barrett's esophagus were most likely to develop high-grade dysplasia or esophageal adenocarcinoma, researchers reported in the April issue of Gastroenterology (2017 Dec 19. doi: 10.1053/j.gastro.2017.12.009).

Those risk factors included sex, smoking, length of Barrett's esophagus, and the presence of baseline low-grade dysplasia, said Sravanthi Parasa, MD, of Swedish Medical Center, Seattle, and her associates. For example, a male with a history of smoking found to have a 5-cm, nondysplastic Barrett's esophagus on histology during his index endoscopy would fall into the model's intermediate risk category, with a 0.7% annual risk of progression to high-grade dysplasia or esophageal adenocarcinoma, they explained. "This model has the potential to complement molecular biomarker panels currently in development," they wrote.

Barrett's esophagus increases the risk of esophageal adenocarcinoma by anywhere from 30 to 125 times, a range that reflects the multifactorial nature of progression and the hypothesis that not all patients with Barrett's esophagus should undergo the same frequency of endoscopic surveillance, said the researchers. To incorporate predictors of progression into a single model, they analyzed prospective data from nearly 3,000 patients with Barrett's esophagus who were followed for a median of 6 years at five centers in the United States and one center in the Netherlands. At baseline, patients were an average of 55 years old (standard deviation, 20 years), 84% were men, 88% were white, and the average Barrett's esophagus length was 3.7 cm (SD, 3.2 cm).

The researchers created the model by starting with many demographic and clinical candidate variables and then by using backward selection to eliminate those that did not predict progression with a *P* value of .05 or less. This is the same method used in the Framingham Heart Study, they noted. In all, 154 patients (6%) with Barrett's esophagus developed high-grade dysplasia or esophageal adenocarcinoma, with an annual progression rate of about 1%. The significant predictors of progression included male sex, smoking, length of Barrett's esophagus, and low-grade dysplasia at baseline. A model that included only these four variables distinguished progressors from nonprogressors with a c statistic of 0.76 (95% confidence interval, 0.72-0.80; *P* less than .001). Using 30% of patients as an internal validation cohort, the model's calibration slope was 0.99 and its calibration intercept was -0.09 cohort (perfectly calibrated models have a slope of 1.0 and an intercept of 0.0).

Therefore, the model was well calibrated and did an appropriate job of identifying risk groups, the investigators concluded. Given that the overall risk of Barrett's esophagus progression is low, using this model could help avoid excess costs and burdens of unnecessary surveillance, they added. "We recognize that there is a key interest in contemporary medical research whether a marker (e.g. molecular, genetic) could add to incremental value of a risk progression score," they wrote. "This can be an area of future research."

There were no funding sources. Dr. Parasa had no disclosures. One coinvestigator disclosed ties to Cook Medical, CDx Diagnostics, and Cosmo Pharmaceuticals.

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SOURCE: Parasa S et al. Gastroenterology. 2017 Dec 19. doi: 10.1053/j.gastro.2017.12.009.

Barrett's esophagus (BE) is the only known precursor lesion to esophageal adenocarcinoma (EAC), a rapidly rising cancer in the Western world, which has a poor 5-year survival rate of less than 20%. Management strategies to affect EAC incidence include screening and surveillance, with current guidelines recommending surveillance for all patients with a diagnosis of BE.


DR. SHARMA

However, there are several challenges associated with adopting BE surveillance for all patients: It is estimated that anywhere from 2 million to 5 million U.S. adults may harbor BE, and the overall risk of BE progression to EAC is low (approximately 0.2%-0.4% annually). Both of these factors influence the cost-effectiveness of a global BE surveillance program.

Hence, a risk-stratification score that can distinguish BE patients who are at high risk for progression to high-grade dysplasia (HGD) and/or EAC from those whose disease will not progress will be extremely useful. This concept would be similar to other risk-scoring mechanisms, such as the MELD score for progression in liver disease.

With use of a large multicenter cohort of patients with BE (more than 4,500 patients), this is the first risk-prediction score developed and validated using baseline demographic and endoscopy information to determine risk of progression. Readily available factors such as patient sex, smoking status, BE length, and confirmed histology were identified as risk factors for progression, which could then generate a score determining the individual patient's risk of progression. Such a simple scoring system has the potential of tailoring management based on the risk factors. In the future, inclusion of molecular biomarkers along with this score may further enhance its potential for personalized medicine in BE patients.

Prateek Sharma, MD, is a professor of medicine of University of Kansas, Kansas City. He has no conflicts of interest.

DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz

Q1. The CagA strain of *Helicobacter pylori* is associated with which of the following?
A. A decreased response to clarithromycin-based therapy
B. A decreased risk of duodenal ulcers
C. A decreased risk of gastroesophageal reflux disease
D. A decreased risk of esophageal squamous cell carcinoma
E. An increased risk of gastric carcinoid tumor

Q2. A 23-year-old man returns from a wedding in Nepal and feels unwell with malaise, low-grade fever, and nausea. He is seen at the student health center at his university. His eyes are noted to be icteric, his mental status is intact, and he is without asterixis. He does not drink alcohol, take medications, or use any supplements. He has no recent sexual partners. He has right upper quadrant tenderness. There are no findings to suggest chronic liver disease. His alanine aminotransferase is 4,150 U/L, his aspartate aminotransferase is 2,132 U/L, bilirubin is 7.8 mg/dL, and he has no INR available. He is then referred urgently to the liver clinic. Additional labs are notable for the following: hepatitis A IgM negative, HBsAg negative, Anti-HBc IgM negative, anti-nuclear antibody negative, anti–smooth muscle antibody negative, and hepatitis E IgM positive.

What is the best next step in the treatment of this patient?
A. Pegylated interferon
B. Ribavirin
C. Observation
D. Entecavir

The answers are on page 24.

Remember the AGA Research Foundation in your will or living trust

What if all you had to do to ensure that the AGA Research Foundation can have an impact for years to come is to write a simple sentence? Sound impossible?

The AGA Research Foundation provides a key source of funding at a critical juncture in the careers of young investigators. Securing the future of the talented investigators we serve really is as simple as writing one sentence. By including a gift to the AGA Research Foundation in your will, you can support our mission tomorrow without giving away any of your assets today.

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How to talk with your patients about PPIs and cognitive decline

A 2018 study published in *Clinical Gastroenterology and Hepatology*, "Lack of association between proton pump inhibitor use and cognitive decline," found no association between PPI use and cognitive decline in analyzing data from two large population-based studies in Denmark. While this data is reassuring, clinicians should continue to anticipate questions from their patients about the risks associated with PPI therapy. AGA recommends the following tips for talking with your patients.

- Reassure patients that you prescribed a PPI for a clear-cut indication, in the lowest possible dose, and for an appropriate period of time (lowest dose, shortest time). This advice echoes that offered by AGA and ABIM in the Choosing Wisely campaign.
- Educate patients not to ask "what side effects do PPIs have?" but rather "is it really indicated?" Reassure patients that, when PPIs are indicated, benefits outweigh risks.
- Keep conversation channels open with patients. When patients require long-term use of PPIs, the medication should not be stopped without a discussion with you about the risks and benefits.
- Recommend that patients also consider life-style modifications that may reduce or eliminate the need for PPIs for long-term use.

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Four new and noteworthy IBD drug studies

Inflammatory bowel disease (IBD) is a vibrant area of clinical research. Many of the 250+ abstracts presented at the inaugural Crohn's & Colitis Congress — a partnership of the Crohn's & Colitis Foundation and AGA — looked at the efficacy and safety of IBD therapies. Below is a summary of four noteworthy drug studies from the Congress, as determined by the Congress organizing committee. You can review all abstracts presented at the Crohn's & Colitis Congress in *Gastroenterology*.

Double-blind, randomized, placebo-controlled, crossover trial to evaluate induction of clinical response in patients with moderate-severe Crohn's disease treated with rifaximin

By Scott D. Lee, University of Washington Medicine, et al.

Significance: It is now known that the intestinal microbiome is integral to the pathogenesis of IBD. However, antibiotic treatments for IBD have previously shown limited effectiveness. In this 8-week clinical trial, there was a fourfold greater response to the antibiotic rifaximin in Crohn's disease treatment, compared with placebo. The positive impact on clinical disease activity was seen even in patients with a significant disease burden and prior exposure to one or more biologic therapies. Quality of life and laboratory measurements were numerically improved. No new safety concerns were identified. These results offer renewed hope for the use of antibiotics in treating Crohn's disease.

Post-hoc analysis of tofacitinib Crohn's disease phase 2 induction efficacy in subgroups with baseline endoscopic or biomarker evidence of inflammation

By Bruce E. Sands, Icahn School of Medicine at Mount Sinai, et al.

Significance: Tofacitinib, a Janus kinase (JAK) inhibitor, is under investigation for treatment of ulcerative colitis and Crohn's disease. To date, response rates in ulcerative colitis have been higher than for Crohn's disease. In this report, investigators performed post-hoc analysis studies using objective baseline criteria of disease activity. Their findings showed a greater proportion of patients with moderate to severe Crohn's disease were in remission with tofacitinib compared to placebo. These results provide evidence of JAK inhibition for the treatment of Crohn's disease and support further investigation.

Refined population pharmacokinetic model for infliximab precision dosing in pediatric inflammatory bowel disease

By Laura E. Bauman, Cincinnati Children's Hospital Medical Center, et al.

Significance: Long-term clinical remission from IBD with anti-TNF therapies has generally been limited to less than half of the treated patients. Improved outcomes are seen with optimal pre-infusion trough drug levels, a measurement of the level of drugs in the patient's bloodstream. However, standard weight-based dosing for pediatric patients has provided widely varying trough drug levels. The investigators report the development of a multifactorial pharmacokinetic model for predicting infliximab trough levels during maintenance therapy for IBD. Such dynamic approaches to treatment address a specific gap in pediatric IBD therapeutic strategies.

Primary nonresponse to tumor necrosis factor antagonists is associated with inferior response to second-line biologics in patients with inflammatory bowel diseases: A systematic review and meta-analysis

By Siddharth Singh, University of California San Diego Health, et al.

Significance: Primary nonresponse to anti-TNF therapy is seen in 35%-65% of IBD patients and another 40%-60% lose responsiveness during the first year of treatment. Physicians struggle with what treatments to recommend for these patients. The investigators in this study performed a literature search and identified eight randomized controlled trials of biologics in patients with prior exposure to anti-TNF and compared outcomes based on their prior responses to anti-TNF. The analysis reveals a 24% decrease in likelihood to achieve remission in patients who changed medications because of immediate nonresponse compared to loss of responsiveness or intolerance during the treatment. These findings raise important questions about the biology of IBD, including the pharmacology of anti-TNF in a subset of patients.

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Better manage acute pancreatitis to improve patient outcomes

AGA has a new clinical guideline on the initial management of acute pancreatitis, published in *Gastroenterology*.

In the U.S., acute pancreatitis is a leading cause of inpatient care among gastrointestinal conditions with more than 275,000 patients hospitalized annually, at an aggregate cost of over $2.6 billion per year.

The guideline focuses on patient care within the first 48-72 hours of admission when management decisions can alter the course of disease and duration of hospitalization.

Guideline recommendations

AGA's new guideline aims to reduce practice variation and promote high-quality and high-value care for patients suffering from acute pancreatitis.

It addresses questions on the benefits of goal-directed fluid resuscitation, early oral feeding, enteral vs. parenteral nutrition, the routine use of prophylactic antibiotics, and routine ERCP in all patients with acute pancreatitis.

The guideline is accompanied by a technical review, a new spotlight (infographic) and a patient companion infographic, which provides key points and important information directly to acute pancreatitis patients.

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AGA's recommendations include:

Statement	Strength of Recommendation	Quality of Evidence
1A. In patients with acute pancreatitis AGA suggests using goal directed therapy for fluid management. *Comment: AGA makes no recommendation whether normal saline or ringer's lactate is used.*	Conditional recommendation	Very low quality
1B. In patients with acute pancreatitis, AGA suggests against the use of hydroxyethyl starch (HES) fluids.	Conditional recommendation	Very low quality
2. In patients with predicted severe acute pancreatitis and necrotizing pancreatitis, AGA suggests against the use of prophylactic antibiotics.	Conditional recommendation	Low quality
3. In patients with acute biliary pancreatitis and no cholangitis, AGA suggests against the routine use of urgent ERCP.	Conditional recommendation	Low quality
4. In patients with acute pancreatitis, AGA recommends early (within 24 hours) oral feeding as tolerated rather than keeping the patient nil per os (NPO).	Strong recommendation	Moderate quality
5. In patients with acute pancreatitis and inability to feed orally, AGA recommends enteral rather than parenteral nutrition.	Strong recommendation	Moderate quality
6. In patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding, AGA suggests either nasogastric or nasoenteral route.	Conditional recommendation	Low quality
7. In patients with acute biliary pancreatitis, AGA recommends cholecystectomy during the initial admission rather than following discharge.	Strong recommendation	Moderate quality
8. In patients with acute alcoholic pancreatitis, AGA recommends brief alcohol intervention during admission.	Strong recommendation	Moderate quality

CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

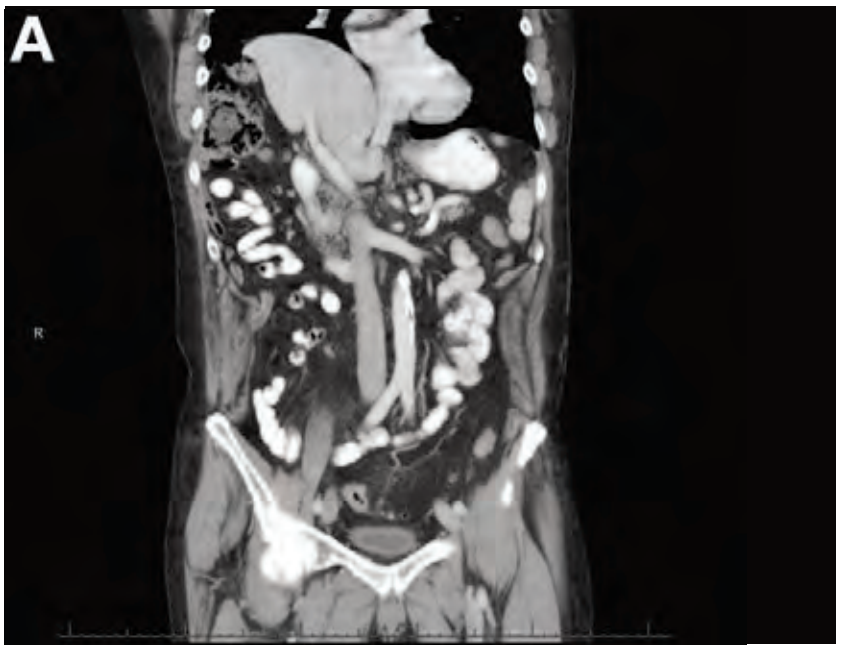
By Jordan Orr, MD, and Charles O. Elson III, MD. Published previously in Gastroenterology (2016;151[2]:241-2).

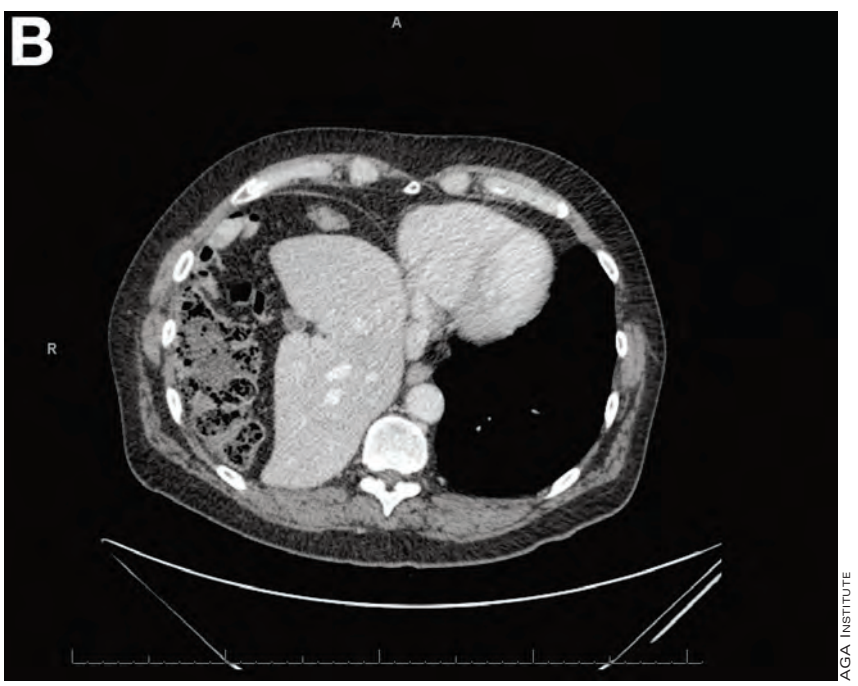
A 67-year-old man presented to the emergency department with complaints of subacute, right-sided flank pain with migratory pain to his right lower quadrant and suprapubic area of increasing intensity for 1 week.

He described his pain as cramping in nature and of fluctuating intensity, acutely worse on the day of presentation. However, within 15 minutes of waiting in the emergency department his pain subsided completely. He further denied any associated nausea, vomiting, diarrhea, melena, hematochezia, dysuria, or hematuria. Vital signs and abdominal physical examination were normal. Further, laboratory testing was unremarkable including a normal urinalysis.

A bedside ultrasound was negative for gallbladder pathology or nephrolithiasis; however, it revealed an abnormal appearing liver. As further diagnostic work up, an abdominopelvic computed tomography scan revealed the following images (Figures A, B). The patient was discharged from the emergency department with scheduled follow-up in the gastroenterology clinic.

The diagnosis is on page 22.





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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Analysis redefined overall illness

Index *from page 1*

A panel of 16 experts then conducted a series of votes to determine which attributes within each domain would be used to assess disease severity. Two sets of attributes were defined as disease markers in Crohn's disease and ulcerative colitis.

A type of conjoint analysis called adaptive choice-based conjoint was then performed to ascertain how different clinical factors influenced specialists' decision making and impressions of disease severity.

A series of questions was asked, with each response determining subsequent questions, until "ample consistency" was found in their choices.

The exercise first had participants decide which hypothetical patient profiles met their evaluation criteria; it then showed them two final profiles and asked which was the more severe case. Survey length depended on the consistency of participants' responses, with those lacking consistency being given more tasks to complete, Dr. Siegel and his colleagues reported.

Respondents completed the exercise three times: first independently without discussion, then after discussion in a group setting with an automated response system, and finally, independently following group discussion.

Disease severity indexes were created on a 100-point scale, and average part-worth utility scores were used to determine minimum and maximum scores for each attribute, with zero representing the absence of a symptom.

Crohn's disease severity was largely dependent on factors related to intestinal damage, whereas ulcerative colitis disease severity was associated with symptoms and effects on daily life.

This analysis "helps redefine overall disease severity for IBD," the authors wrote. Once validated, the indexes will offer "both further research opportunities and a practical tool by which to classify overall disease severity of patients and offer appropriate treatment without relying on present symptoms alone," they added.

Disease severity indexes were created on a 100-point scale, and average part-worth utility scores were used to determine minimum and maximum scores for each attribute, with zero representing the absence of a symptom.

Dr. Siegel and his colleagues noted that future studies should focus on prospective validation of the disease indexes in different patient populations, as well as conducting a conjoint analysis with patients.

"We expect this work to begin to address a change in how we think about patients with IBD and how to identify those at the higher end of the risk spectrum so that appropriate intensive treatment can be initiated and optimized in an efficient, precise, and cost-effective manner," they concluded.

The study was funded by AbbVie and Tillotts Pharma. The authors disclosed financial relationships with numerous additional pharmaceutical companies.

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SOURCE: Siegel CA et al. Gut. 2018 Feb;67(2):244-54.

AGA resource
AGA patient education materials can help your IBD patients better understand and manage their disease. Learn more at www.gastro.org/IBD.

AGA Clinical Practice Update

Psych care *from page 1*

the scientific rationale and best practices associated with incorporating brain-gut psychotherapies into routine GI care. Furthermore, it presented recommendations on how to address psychological issues and make effective referrals in routine practice.

Previous studies had highlighted that the burden of chronic digestive diseases is amplified by psychosocial factors, including poor coping, depression, and poor social support. Mental health professionals specializing in psychogastroenterology integrate the use of brain-gut psychotherapies into GI practice settings, which may help reduce health care utilization and symptom burden.

The article contained best practice advice based on a review of the literature, including existing systematic reviews and expert opinions. These best practices include the following:

- Gastroenterologists routinely should assess health-related quality of life, symptom-specific anxieties, early-life adversity, and functional impairment related to a patient's digestive complaints.
- Gastroenterologists should master patient-friendly language to help explain the brain-gut pathway and how this pathway can become dysregulated by any number of factors, the psychosocial risks perpetuating and maintaining factors of GI diseases, and why the gastroenterologist is referring a patient to a mental health provider.
- Gastroenterologists should know the structure and core features of the most effective brain-gut psychotherapies.
- Gastroenterologists should establish a direct referral and ongoing communication pathway with one or two qualified mental health providers and assure patients that they will remain a part of the care team.
- Gastroenterologists should familiarize themselves with one or two neuromodulators that can be used to augment behavioral therapies when necessary.

Patient education about the referral to a mental health provider is difficult and requires attention to detail and fostering a good physician-patient relationship. It is important to help patients understand why they are being referred to a psychologist for a gastrointestinal complaint and that their physical symptoms are not being discounted. Failure to properly explain the reason for referral may lead to poor follow-through and even lead the patient to seek care with another provider.

In order to foster widespread integration of these services, research and clinical gaps need to be addressed. Research gaps include the lack of prospective trials that compare the relative effectiveness of brain-gut psychotherapies with each other and/or with that of psychotropic medications. Other promising brain-gut therapies, such as mindfulness meditation or acceptance-based approaches, lack sufficient research to be included in clinical practice. Limited evidence supports the effect that psychotherapies have in accelerating or enhancing the efficacy of pharmacologic therapies and on improving disease course or inflammation in conditions such as Crohn's disease and ulcerative colitis.

Clinical gaps include the need for better coverage for these therapies by insurance – many providers are out of network or do not accept insurance, although Medicare and commercial insurance plans often cover the cost of services in network. Health psychologists can be reimbursed for health and behavior codes for treating these conditions (CPTs 96150/96152), but there are restrictions on which other types of professionals can use them. Ongoing research is focusing on the cost-effectiveness of these therapies, although some highly effective therapies may be short term and have a one-time total cost of $1,000-$2,000 paid out of pocket. There is a growing need to expand remote, online, or digitally based brain-gut therapies with more trained health care providers that could offset overhead and other therapy costs.

The authors state they have no conflicts of interest.

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SOURCE: Keefer L et al. Gastroenterology. 2018. doi: 10.1053/j.gastro.2018.01.045.

Tofacitinib: FDA panel recommends UC indication

BY IAN LACY
Frontline Medical News

Federal advisors to the Food and Drug Administration on March 8 voted unanimously to recommend approval of an additional indication for tofacitinib (Xeljanz), this time for ulcerative colitis (UC).

Members of the Gastrointestinal Drugs Advisory Committee unanimously voted to recommend two different dosing regimens: 10 mg twice daily for 16 weeks in patients who have not experienced a therapeutic benefit after 8 weeks of treatment, as well as 10 mg twice daily for patients who have an inadequate or loss of response to TNF-blocker therapy, based on the results of several phase 3 clinical trials.

AGA resource
Visit www.gastro.org/IBD for patient education guides that you can share with your ulcerative colitis patients.

The committee rejected by a 7-8 vote a recommendation that Pfizer, the drug's manufacturer, conduct a postmarketing efficacy trial comparing a 10-mg continuous dosing regimen with one that has a 10-mg induction dose then a 5-mg twice-daily maintenance dose.

The recommended UC indication was based on the OCTAVE trials (N Engl J Med. 2017;376:1723-36), including a phase 2 study; two identical phase 3 induction trials (OCTAVE Induction 1 and OCTAVE Induction 2); a 53-week, phase 3 maintenance trial (OCTAVE Sustain); and an open-label extension study.

The induction trials enrolled a total of 1,139 patients with moderate to severe UC. Patients in both studies were administered tofacitinib 10 mg twice daily or placebo and were assessed after 8 weeks to judge clinical response. Patients in both studies displayed notable remission rates (18.5% and 16.6%), compared with placebo, according to Eric Maller, MD, executive director of the UC development program at Pfizer.

Patients who did not achieve remission but showed some clinical response (decrease in Mayo score of at least 3 points) were then enrolled in the 53-week OCTAVE Sustain, where they were randomized to receive tofacitinib 10 mg twice daily, 5 mg twice daily, or placebo.

During maintenance treatment, both 5-mg and 10-mg doses showed substantial treatment benefits, with 32.4% and 41.0% of patients achieving remission, an increase of 22.0% and 30.7%, compared with placebo, respectively.

As part of the maintenance study, Pfizer analyzed patients with or without prior TNF-blocker failure. This analysis revealed that patients who had previously failed TNF-blocker therapy experienced a greater treatment benefit than those who had not. While the benefit was noticeable in both dosage groups, patients taking the 10-mg dose experienced the greatest benefit, with a 70% increase in remission rates, 39% increase in mucosal healing, and 75% increase in steroid-free remission among baseline remitters, compared with patients in the 5-mg group, Dr. Maller said.

Researchers also looked at a subgroup of 295 patients who had no clinical response to tofacitinib 10 mg twice daily after 8 weeks and subsequently treated them for an additional 8 weeks as part of an open-label extension study. After the additional 8 weeks of treatment, over half (51.2%) displayed clinical responses and 8.6% were in remission.

"This is a desperate patient population. These are impressive results," stated Darrell Pardi, MD, vice chair of the advisory committee and a professor of medicine at the Mayo Clinic, Rochester, Minn.

Serious adverse events were seen in 4% of tofacitinib-treated patients in the induction trials, compared with 6% of placebo-treated patients, according to Lesley Hanes, MD, medical officer with the FDA Center for Drug Evaluation and Research.

Adverse events appeared to be dose dependent, with risk of deaths and malignancies (excluding nonmelanoma skin cancer), opportunistic infections, herpes zoster infection, "possible" drug-induced liver injury, and cardiovascular and thromboembolic events more commonly occurring with the 10-mg dose, Dr. Hanes said. According to Dr. Pardi, "Several of these are mitigatable by dermatologic exam or, hopefully, a vaccine."

Several of the advisory committee members submitted conflict of interest waivers. Chair Jean-Pierre Raufman, MD, and vice chair Darrell Pardi, MD, disclosed funding from competing pharmaceutical manufacturers.

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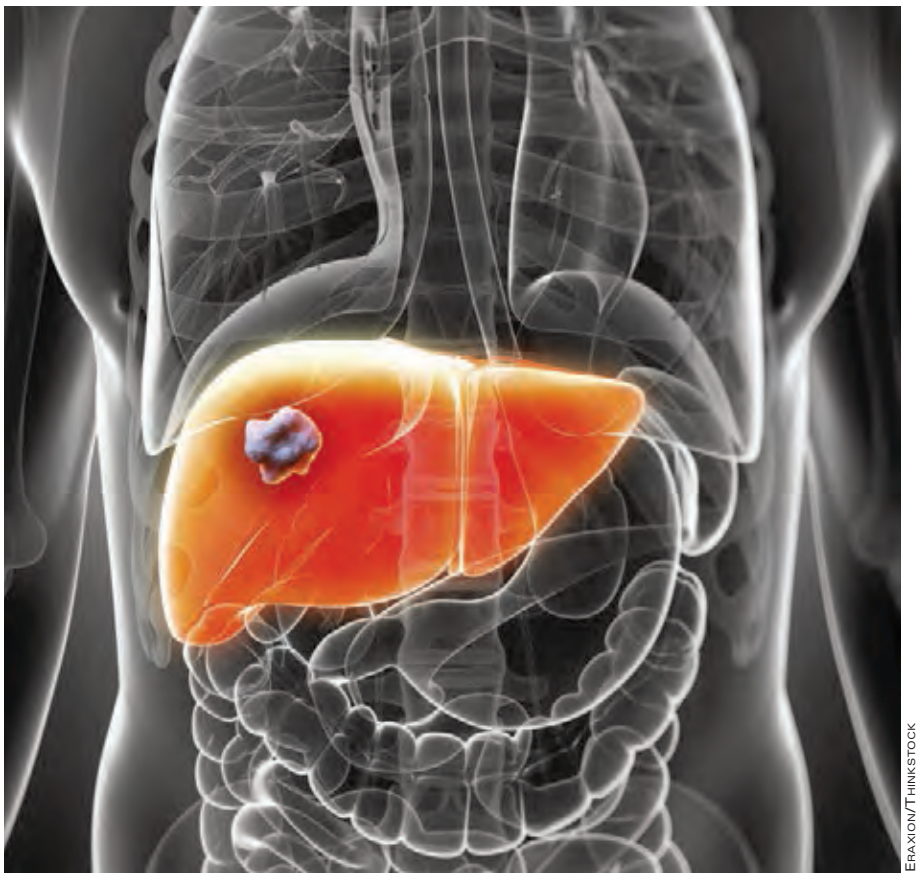
Screening will be important

NASH *from page 1*

Transplantation Network, shows that the prevalence of HCV has been in steady decline since 2005 and that decline is forecast to continue. From a prevalence of 3.22 million cases in 2005, researchers have forecasted a decline to 1.06 million cases by 2025.

At the same time, even a conservative linear model for the changing prevalence of NASH forecast a rapid increase from 1.37 million cases in 2005 to 17.95 million in 2025. The exponential model suggested an increase from 2.41 million in 2005 to 42.34 million in 2025.

In terms of the effect on the prevalence of hepatocellular carcinoma (HCC), the modeling suggested cases of HCV-related liver cancer were predicted to peak at around 29,000 cases in 2015 then decline to fewer than 18,000 cases by 2025. In contrast, the prevalence of HCC from NASH is forecast to increase from between 5,000 and 6,000 cases in 2005 to 45,000 in 2025 by the conservative linear model or even as high as 106,000 cases according to the exponential model. It overtook HCV infection as a cause of liver cancer by around 2015.



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"Despite the lack of existing data off of which to work, the general trends of our prediction models are consistent with the documented trends of liver transplant etiology, as well as 2010 insurance data indicating nonalcoholic fatty liver disease/NASH as the leading etiology associated with HCC," wrote Osmanuddin Ahmed, MD, from the Rush University Medical Center in Chicago and his coauthors.

The study used liver transplant data as a proxy for the prevalence of hepatocellular carcinoma and also took into account the natural history of the disease. Between 5% and 20% of untreated HCV infections will go on to develop into cirrhosis, and of patients with HCV-related cirrhosis, around 15% will develop HCC within 10 years. In the case of NASH, the authors cited research suggesting that around 35% of patients go on to develop progressive fibrosis, that progression to cirrhosis takes around 29 years, and that the risk of progression to HCC ranged from 2.4% over 7 years to 12.8% over 3 years.

"A higher proportion of patients with NASH develop cirrhosis, but of those who develop cirrhosis, the probability of developing HCC is higher in patients with HCV," the authors wrote. "In contrast, HCV progression to HCC rarely occurs in noncirrhotic patients."

The authors wrote that it was important to explore projected trends in the etiology of hepatocellular carcinoma to inform the development of screening, diagnostic, and treatment approaches, particularly given potential differences in the pathology, natural history, and treatment options for NASH-related and HCV-related liver cancer.

"Histologically, NASH shares characteristics with alcoholic liver disease, primarily proinflammatory fat accumulation in parenchymal cells, [and] key players in NASH progression to HCC are suggested to include genetic modifications, proinflammatory high-fat and/or high-fructose diets, and oxidative and endoplasmic cellular stresses," they wrote. "In HCV progression to HCC, the presence of the HCV core protein may induce HCC without the prerequisite load of genetic errors normally required for cancer development, skipping or accelerating some of the classic steps of cancer induction."

The authors did note that their model represented a base scenario that assumed the environmental and genetic factors driving NASH would continue along the path of current trends.

"Therefore, the possibility exists that our models underestimate the response of the medical community in addressing the rising nonalcoholic fatty liver disease/NASH epidemic."

No funding sources or conflicts of interest were declared.

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SOURCE: Ahmed O et al. J Clin Exp Hepatology. 2018 Feb 24. doi: 10.1016/j.jceh.2018.02.006.

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" on page 12: Chilaiditi syndrome

Abdominal CT images display the Chilaiditi sign, which is the radiographic term used to describe interposition of the colon, usually at the hepatic flexure, with the liver and right diaphragm.[1] This is considered an incidental radiographic finding and is generally asymptomatic; however, when one develops clinical symptoms such as abdominal pain, bloating or distension, anorexia, constipation, or nausea, it is called Chilaiditi syndrome. First described by Greek radiologist Demetrius Chilaiditi in 1910, Chilaiditi syndrome is a rare occurrence with an incidence rate of 0.25%-0.28% in the general population.[2] The etiology of Chilaiditi syndrome is felt to be congenital or acquired with predisposing congenital abnormalities such as absent suspensory or falciform ligaments, redundant colon, malposition of the colon, dolichocolon, and paralysis of the right diaphragm. Other risk factors for development of Chilaiditi syndrome include chronic constipation, cirrhosis, ascites, and obesity. Men are four times as likely as women to develop Chilaiditi syndrome and it is more common in the elderly, occurring in 1% of the elderly population.[3] Chilaiditi sign is diagnosed with radiographic imaging meeting the following criteria: The right hemidiaphragm must be elevated above the liver by the intestine, the bowel must be distended by air to illustrate pseudopneumoperitoneum, and the superior margin of the liver must be depressed below the level of the left hemidiaphragm.[1]

Chilaiditi syndrome is managed conservatively with close observation. Recurrent symptoms can be treated with colopexy. This syndrome has been known to cause severe complications including volvulus of the cecum, splenic flexure, or transverse colon, cecal perforation, and subdiaphragmatic perforated appendicitis, which all require surgical intervention.[3] It is important to recognize Chilaiditi syndrome on presentation to prevent unnecessary diagnostic studies and unwarranted surgical intervention.

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GI & HEPATOLOGY NEWS

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Nonendoscopic nonmalignant polyp surgery increasing

BY ELI ZIMMERMAN
Frontline Medical News

Rate of nonendoscopic surgeries for nonmalignant colorectal polyps significantly increased from 5.9 to 9.4 per 100,000 people from 2000 to 2014, according to a study in Gastroenterology.

These surgeries are not only associated with a much higher risk to patients than endoscopic procedures, but they also are significantly less cost effective, which confused investigators as to the cause of the increase.

"The literature to date is clear that endoscopic resection is the preferred management of nonmalignant colorectal polyps," Anne Peery, MD, a gastroenterologist at the University of North Carolina at Chapel Hill, and her colleagues explained. "Among patients who have surgery for a nonmalignant colorectal polyp, 14% will have at least one major short-term postoperative event."

Data from 1,230,458 surgeries conducted during 2000-2014 and recorded in the Healthcare Cost and Utilization Project National Inpatients Sample were included in this study. Patients who underwent a nonendoscopic procedure for nonmalignant polyps were predominantly non-Hispanic white, covered by Medicare, from the highest household income range, and aged 66 years on average.

While non-Hispanic white patients had the highest overall rate increase by ethnicity, rising from 5.6 to 10.5 per 100,000 population, rates in non-Hispanic black and Hispanic patients also rose significantly, increasing from 3.5 to 5.8 per 100,000 population and from 1.1 to 3.7 per 100,000 population, respectively.

Regionally, rates of surgery were higher in the Midwest (10.8 per 100,000) and the South (10.6 per 100,000) than in the Northeast (7.8 per 100,000) and West (7.5 per 100,000). Incidence rates rose equally for both men and women.

Large urban teaching hospitals were found to have the largest rate increase when data were stratified by teaching status. "We had hypothesized that surgery for nonmalignant colorectal polyps would be both uncommon and declining in teaching hospitals where providers are more likely to be familiar with current guidelines and to have access to endoscopic mucosal resection," wrote the investigators.

The investigators first hypothesized the increased rate seen in teaching hospitals could be caused by a higher concentration of case referrals to these high-volume centers, following a trend of centralizing cancer procedures. However, there has been no other sign that colon and rectal cancer procedures are following this trend.

Another option considered by Dr. Peery and her colleagues was that the increased procedures may stem from a rise in colorectal cancer screening; however, the data indicate screenings did not change from 2010 to 2015, leaving investigators with few final guesses to go on.

"It is also conceivable that increasing production pressure and inadequate reimbursement for endoscopic mucosal resection may persuade endoscopists to refer patients with complex nonmalignant colorectal polyps for surgery," said Dr. Peery and fellow investigators. "Finally, there is the issue of risk ... for endoscopists without additional training in advanced endoscopic resection, these risks may be perceived as too great, especially when they have the option of referring for a surgical resection."

The investigators reported no relevant financial disclosures.

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SOURCE: Peery A et al. Gastroenterology. 2018 Jan 6. doi: 10.1053/j.gastro.2018.01.003.

PERSPECTIVE

Management of complex colon polyps

In this comprehensive analysis, Peery et al. found a rising incidence of surgery for nonmalignant colorectal polyps despite relatively stable colorectal cancer screening rates and with decreasing incidence of colorectal cancer surgery.

In a separate study, the authors found that 14% of patients who underwent surgical resection of nonmalignant colorectal polyps had a major postoperative event. Other population-based studies have reported similar incidence of surgical complications.

This report thus raises concern for inappropriate surgical referral. While reimbursement models may play a role, many factors are involved with surgical referral. Complex polypectomy, often using endoscopic mucosal resection techniques to remove large polyps, is associated with higher rates of bleeding, perforation, and incomplete resection, compared with standard polypectomies. The decision to refer to surgery or to attempt endoscopic resection is based on provider experience and polyp characteristics, including suspicion for malignancy. Current literature suggests that surgical removal is recommended less frequently by specialists in complex polypectomy, compared with nonspecialists.


DR. KETWAROO

Given this study's findings, health systems should consider including surgical referral rates in their quality measures. Thus, high-quality endoscopy centers would ensure that complex polyps are appropriately characterized and initially managed by endoscopists experienced in complex polypectomy. This is especially important with the increasing repertoire of endoscopic alternatives to surgery that we can offer our patients.

Gyanprakash A. Ketwaroo, MD, MSc, is anassistant professor, division of gastroenterology and hepatology, Baylor College of Medicine, Houston. He has no conflicts.

DDSEP eight
Digestive Diseases Self-Education Program

Quick Quiz Answers

Q1. Correct Answer: C

Rationale
The CagA strain of *Helicobacter pylori* has been associated with an increased risk of gastric adenocarcinoma and MALT lymphoma. CagA-producing *H. pylori* infection also causes more severe mucosal inflammation and is associated with higher incidences of gastric and duodenal ulcers. A protective effect of CagA+ *H. pylori* against gastroesophageal reflux disease, reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma has been suggested, because some epidemiologic studies have shown a decreased prevalence of these disorders. Further studies are needed to verify these relationships, but no studies to date have demonstrated an increased risk of esophageal carcinoma associated with *H. pylori*. CagA-producing *H. pylori* has not been associated with gastric carcinoid tumor.

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Q2. Correct Answer: C

Rationale
This patient has contracted acute hepatitis E while traveling to Nepal, as evidenced by the positive hepatitis E IgM. Infection is most likely derived from fecal contamination of water. Hepatitis E genotype 1 (HEV1) is most common in Asia. Infections may range from asymptomatic to symptomatic. Symptoms may include nausea, anorexia, abdominal pain, myalgias, and fatigue. Liver enzyme elevations are variable. The highest mortality rates occur in the third trimester of pregnancy, young children, and in those with preexisting chronic liver disease. In immunocompetent hosts, HEV infection is generally self-limited and does not require specific treatment; therefore observation is the best treatment.

Reference
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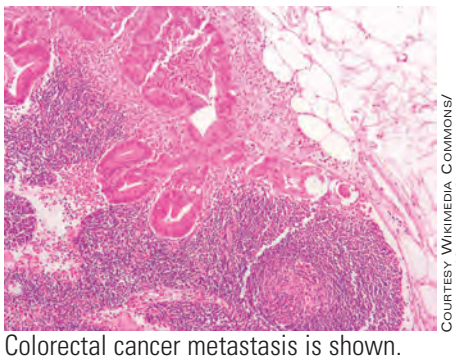
Colorectal cancer risk stratification enhanced by combining family history and genetic risk scores

BY TERRY L. KAMPS
Frontline Medical News

Stratification of colorectal cancer (CRC) risk was enhanced by joint consideration of the independent family history and genetic risk score predictors, according to an ongoing population-based, case-control study of patients recruited during 2003-2010.

The research was conducted using data from DACHS (Colorectal Cancer: Chances for Prevention Through Screening), an ongoing population-based, case-control study in Germany, reported Korbinian Weigl, PhD, and his colleagues in the journal Clinical Epidemiology (doi: 10.2147/CLEP.S145636). They included 2,363 eligible CRC patients who were identified by 22 participating hospitals and frequency matched with respect to sex, age, and residential location to 2,198 randomly selected controls who had genome-wide association studies data. The population consisted of 40% women, and the median ages for cases and controls were 69 and 70 years, respectively.



Courtesy Wikimedia Commons/Nephron/Creative Commons

Colorectal cancer metastasis is shown.

Genetic risk score was calculated by genotyping 53 single-nucleotide polymorphisms reported in published literature to be associated with higher CRC risk for individuals of European descent. Seven genetic risk score groups – very low, low, low-medium, medium, medium-high, high, and very high – were established according to categories generated on the basis of weighted risk allele distribution among controls. Family history referred to CRC in first-degree and second-degree relatives. Selected potential confounders included age, sex, body mass index, education, hormone replacement therapy in women, smoking, and colonoscopy history. Odds ratios with 95% confidence intervals were estimated by multiple logistic regression models that included adjustment for potential confounders. Statistical calculations examined individual and joint family history and genetic risk score associations with risk for CRC and the effect of potential confounding factors.

At least one colonoscopy was performed on over half the individuals in the control group, while a significantly lower number (*P* less than .0001) were performed on case individuals (22.1%). Family history of CRC in first-degree relatives was reported by 316 case participants (13.4%) and 214 controls (9.7%; *P* less than .0001). The calculated genetic risk score ranged from 20 to 48, with a substantially higher proportion of cases in the higher deciles.

Investigators compared the risk for CRC in the top decile with that in the lowest and found an increased risk of 2.9-fold (OR, 2.94) based on

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PRACTICE MANAGEMENT TOOLBOX: Cracking the clinician educator code in gastroenterology

BY JORDAN M. SHAPIRO, MD, MILENA GOULD SUAREZ, MD, AND TERI LEE TURNER, MD, MPH, MED


DR. SHAPIRO


DR. GOULD SUAREZ


DR. TURNER

For gastroenterologists who enter academic medicine, the most common career track is that of clinician educator (CE). Although most academic gastroenterologists are CEs, their career paths vary substantially, and expectations for promotion can be much less explicit compared with those of physician scientists. This delineation of different pathways in academic gastroenterology starts as early as the fellowship application process, before the implications are understood. Furthermore, many community gastroenterologists have appointments within academic medical centers, which typically fall into the realm of CEs.

A review of all gastroenterology and hepatology fellowship program websites listed on the American Gastroenterological Association website showed that 33 of 175 (18.8%) programs endorse distinctly different tracks, usually distinguishing traditional research (i.e., basic science, epidemiology, or outcomes) from clinical care of patients (i.e., CE or clinical scholar). One of the most common words appearing in descriptions of both tracks was "clinical," highlighting that a good CE or researcher is, first and foremost, a good clinician.

With clinical duties requiring the majority of a CE's time and efforts, a reasonable assumption is that CEs are clinicians who teach trainees via lectures, clinic, endoscopy, and/or inpatient rounds. Included in the category of CE are community clinicians who have a stake in the education of residents and fellows. Sherbino et al[1] defined a CE as "a clinician active in health professional practice who applies theory to education practice, engages in education scholarship, and serves as a consultant to other health professionals on education issues."

Content from this column was originally published in the "Practice Management: The Road Ahead" section of Clinical Gastroenterology and Hepatology (2017;15:1828-32).

Because we recognize that many community and academic gastroenterologists spend the majority of their education efforts teaching trainees, we have made every effort to ensure that the five recommendations listed later are equally pertinent to all gastroenterologists who devote any portion of their careers to educating trainees, colleagues, allied health professionals, or patients. For example, a CE who primarily teaches trainees still can benefit from learning how to better document their efforts, receive mentorship as an educator, take everyday activities and convert them into scholarship, share teaching materials with broader audiences, and learn new teaching techniques without ever opening a book on education theory. For community-based physicians, this can assist in obtaining recognition from academic centers for their teaching efforts.

Number 1: Maintain a current curriculum vitae and teaching portfolio

All CEs must have two critical instruments to document their accomplishments to their institutions and to the field: a curriculum vitae (CV) and a teaching portfolio. These items also are very important when the time comes for promotion because they validate one's accomplishments, both quantitatively and qualitatively. Knowing the criteria for promotion as a CE is critical for shaping one's career, and we recommend checking with an individual's institution for its specific requirements regarding formats for both the CV and the teaching portfolio, which typically are available from the academic promotion committee. Because most fellows and faculty are familiar with the format of a CV, we will focus on the teaching portfolio.

For most fellows and many faculty, the teaching portfolio is a new and/or less well understood entity. Unlike a CV, the teaching portfolio presents teaching activities not only as a collection or list, but also provides evidence of the influence the work has had on others, in a much more personal way. A few tips are listed on putting together a teaching portfolio. However, the most important advice we can offer is this: one should save all evidence of teaching including unsolicited letters and e-mails from learners and colleagues.

If your institution does not have a teaching portfolio template, we recommend using a pre-existing format. Several examples from academic medicine can be found on the Internet or on MedEdPORTAL, an open-access repository of educational content provided by the Association of American Medical Colleges. One such tool is the Educator Portfolio Template of the Academic Pediatric Association's Educational Scholars Program (available: www.academicpeds.org/education/educator_portfolio_template.cfm). The Association of American Medical Colleges Group on Education Affairs held a consensus conference in 2006, from which five educational categories were defined: teaching, learner assessment, curriculum development, mentoring and advising, and educational leadership and administration.[2] These categories can serve as an arrangement for a teaching portfolio. We also recommend that you include both educational research/scholarship and web-based educational materials such as online learning modules, YouTube videos, blogs, and wikis as a part of a

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genetic risk analysis adjusted for sex and age and an increased risk of 3.0-fold (OR, 3.0) when all other covariates except family history were included. Comparing results against analysis with the 27 single-nucleotide polymorphisms that had been used in previous studies indicated a sizable improvement in genetic risk stratification as a result of increasing the number of single-nucleotide polymorphisms (*P* value for increase in c statistic = .003) included in the analysis.

Risk associated with having a family history of CRC in a first-degree relative was 1.5-fold (OR, 1.47) higher in an age- and sex-adjusted analysis. Risk prediction increased to an OR of 1.86 when calculations were adjusted with covariates, especially with previous colonoscopies. Using genetic risk scoring as a calculation adjustment only slightly changed the result (OR, 1.83). A similar trend, but with lower-magnitude associations, was observed with family history of CRC in second-degree relatives.

A dose-response association between the number of risk alleles and CRC risk determined by a logistic regression model revealed a curvilinear relationship between genetic risk score and CRC risk. At higher genetic risk score levels, the increase in CRC risk was particularly strong. The dose-response association indicated an independent relationship between family history and CRC such that individuals with first-degree relatives with CRC will reach the same risk level with a lower genetic risk score as those with a higher genetic risk score but no first-degree relatives with CRC.

Joint risk stratification that combined family history and genetic risk scores was compared with risks determined by each predictor. As the genetic risk score increased there was an observed increased risk for individuals with first-degree relatives, second-degree relatives, or without family history. Considering only genetic risk score, the increase in risk from the lowest to highest decile was 2.8-fold. In contrast, the increased risk from the lowest to highest decile was 6.14-fold when stratification included both genetic risk score and considering family history in first-degree relatives, thus demonstrating the enhancing effect of combining the independent relationship of these two predictors.

The investigators concluded from their results that, by combining the genetic risk scores with family history and other easy-to-collect risk factor information, this approach "provided more accurate risk stratification than stratification based on each of these variables individually."

The authors reported that they had no conflicts of interest.

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SOURCE: Weigl K et al. Clin Epidemiol. 2018;10:143-52.

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teaching portfolio. For each project highlighted in the teaching portfolio, we recommend reflecting on and writing down how the project shows the quantity and quality of the work.

Quantity of work in the teaching portfolio refers to more than a mere cataloging of published peer-reviewed articles and book chapters, courses taught, presentations given, and so forth (which should be included in the CV). Instead, it documents time spent in teaching activities, how often teaching occurs, the number and types of learners involved, and how the activity fits into a training program.

Quality of work can include how innovative methods were crafted and implemented to customize teaching in creative ways to accomplish specific learning objectives. When documenting evidence of quality, provide comparative measures whenever possible. Quality of teaching also can be illustrated by evaluations, pretests and posttests, and as complimentary e-mails and letters from learners and other faculty members. The description of teaching activities also shows one's flexibility as an educator, and the greater the breadth of experiences, the better. A CE also must document within the portfolio how the teaching activity drew from existing literature and best practices and/or contributed to the medical education field. .

The teaching portfolio templates begin with a personal statement outlining why one teaches. It is important to include details of how impact was defined or determined with regard to teaching endeavors, how the feedback from formal evaluative processes was used to mold one's future activities as an educator, and what strategies will be implemented to improve teaching to meet the needs of diverse and changing groups of learners.

Both the CV and teaching portfolio should be updated continually – we recommend at least quarterly (or as articles are published, courses are taught, abstracts are presented, and so forth) – to ensure that nothing is overlooked or forgotten.

Number 2: Mentors and mentees

Every CE needs to have a primary mentor, typically a more senior faculty member with an interest in and experience with mentoring, as well as a commitment to fostering the mentee's professional growth. It may be difficult to find a mentor when starting out as a junior faculty member or when changing academic institutions. Once you have a mentor, take ownership for the success of the relationship by managing-up, by organizing all the meetings, exceeding (not just meeting) deadlines, and by communicating

Take-away points

1. Think broadly about education scholarship: many day-to-day activities can count twice and be transformed into scholarship.
2. Start and routinely update a teaching portfolio to demonstrate the quantity and quality of education scholarship.
3. Engage in local and national opportunities to grow as a clinician educator.
4. Become familiar with different forums to share educational scholarship.

needs and information in a way the mentor prefers. Rustgi and Hecht[3] wrap up their article on mentorship with a pathway that highlights the following components for a successful mentoring relationship: regular meetings, specific goals and measurable outcomes, manuscript and grant writing, presentation skills, and navigating the complexities of regulatory affairs such as institutional review boards. Although many of these tenets hold true for both clinician researchers and CEs, Farrell et al[4] offer four steps to finding a mentor for CEs, as follows. Step 1: self-reflection and assessment: critically assessing one's competence as a teacher, educational administrator, or researcher; determining what prior education projects have been successful and why; and defining career goals. Step 2: identification of areas needing development: examples may include teaching skills, curriculum innovation, evaluation/assessment, educational research, time management, negotiation skills, grantsmanship, scholarly writing, and presentation skills; identify specific questions regarding the type of help needed. Step 3: matchmaking: determine qualities (personal and professional) desired in a mentor, and search for candidates with the help of colleagues. Step 4: engagement with a mentor: explain why you desire mentorship, career goals, current academic role(s), your perceived needs, and recognize and acknowledge appreciation for your mentor's time and energy.

One caution is to avoid having too many primary mentors. Although having clinical, research, and/or personal mentors can be helpful, having too many mentors can make it difficult to meet regularly enough to allow for the mentee–mentor relationship to grow. Instead of a network of mentors, build a web of minimentors to serve as consultants, coaches, and accountability partners, and tap into this network as needed. Mentors are involved longitudinally with mentees and tend to provide general career and project-specific guidance, whereas coaches tend to be involved in specific projects.

In addition to having their own mentors, CEs quickly will find opportunities themselves to serve as mentors to more junior faculty, fellows, residents, and students.

Number 3: Think broadly about scholarship

Traditionally, the definition of scholarship has been very narrow and usually is related to the number of publications and grants one receives. Beginning with Boyer's work in 1990, the definition of scholarship has expanded at academic institutions beyond the concept of traditional research.[5] Medical education scholarship most often is guided and judged by six core qualitative standards of excellence, known as "Glassick's criteria"[6]: clear goals, adequate preparation, appropriate methods, significant results, effective presentation, and reflective critique. The key to scholarship is that it builds on or adds to the field, is made public, and thus available for peer-review.

CE projects can be categorized in many ways, but we recommend broadening the classic notions of research with which we have been indoctrinated. Golub's[7] 2016 editorial in the Journal of the American Medical Association, "Looking Inward and Reflecting Back: Medical Education and Journal of the American Medical Association," highlights the range of research questions and methodolo-

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gies, which include ethics, behavioral psychology, diversity of patient care and the workforce, medical education research, quality and value of care, well-being of trainees and faculty, and health informatics. If one breaks down daily tasks, countless opportunities for scholarly projects will emerge. One need look no further than the opportunities for quality improvement research that avail themselves daily, with examples ranging from reducing variation in cirrhosis care to improving adenoma detection rates. Quality improvement is an important method of scholarship for both academic and community-based physicians, which also can contribute toward Part IV of Maintenance of Certification requirements. CEs also can engage in educational scholarship other than research by using these same principles. To transform your teaching into scholarship you should examine the activities you perform or a problem that needs to be solved, apply information or a solution based on best practices or what is known from the literature, and then share the results/products with others (peer-review). Crites et al[8] provide practical guidelines for developing education research questions, designing and implementing scholarly activities, and interpreting the scope and impact of education scholarship.

In addition, reaching beyond one's department to other departments, as well as participating in educational scholarly activities on regional and national levels, is important as one's career progresses. Well-connected and diverse networks are information highways by which one's work can be amplified to achieve a greater impact, and from which many opportunities will be shared.

Table 1. Pathways for educator development

Level	Focus	Examples
All levels		American Gastroenterological Association Academy of Educators is a resource for all levels of clinician educators: *http://www.gastro.org/about/initiatives/aga-academy-of-educators*
Beginner	Improving teaching skills in the clinical setting	Book: Clinician-Educator Handbook: *https://media.bcm.edu/documents/2014/84/clinicianedhandbook.pdf* Online modules (particularly feedback, 1-minute preceptor, and evaluating your student): *https://www.med-ed.virginia.edu/courses/fm/precept/index.htm* Live courses or webinars: faculty development GME Ichan School of Medicine at Mount Sinai: *https://www.youtube.com/channel/UCI23qEame4hvIWPI3Mi8dbA* Grand rounds, workshops, or educational seminars at home institution or regional/national meeting
Intermediate	Building your teaching repertoire by learning about the science of medical education	Essential Skills in Medical Education online course: *https://amee.org/amee-initiatives/esme-courses/amee-esme-online-courses/esme-online* Harvard Macy Institute live courses: *http://www.harvardmacy.org/* Coursera online course (i.e., Instructional methods in Health Professions Education): *https://www.coursera.org/learn/instructional-methods-education* Longitudinal teacher training programs at home institution (i.e., Master Teacher Fellowship)
Advanced	Applying the science of education to the clinical teaching setting and obtaining an advanced degree	Certificate or degree programs in medical education — current listing can be found at: *http://www.aacom.org/one/profdev/fac-dev/degree-programs* The Association of Medical Educationin Europe MedEdWorld Webinars: *http://www.amee.org/amee-initiatives/mededworld/webinars* Resources for medical education research and scholarship: *http://omerad.msu.edu/chmeducator/meded_research_scholarship.html* Association of American Medical Colleges Medical Education Research Certificate program: *https://www.aamc.org/members/gea/merc/*

Note: Developed by Dr. Turner.

Number 4: Share broadly

Scholarship activities of both academic and community-based CEs can target many audiences, including medical students, residents, and fellows; faculty; other health professions; or even patients and the community. Knowing who will be the recipients or end-users can help to identify which types of projects may be most rewarding and make the greatest impact. Consider sharing curricula, evaluation tools, and other educational products with colleagues at other institutions who ask for them. Request acknowledgment for the development of the materials and ask for written feedback on how these products are being used.

One education model used to assess the impact and target of education interventions is known as Kirkpatrick's[9] hierarchy, which traditionally included the following four levels: reaction (level 1), learning (level 2), behavior (level 3), and results (level 4). The model has been adapted by the British Medical Journal's Best Evidence in Medical Education collaboration to medical education with the following modifications in levels as follows.[9,10] Level 1: participation: focused on learners' views of the learning experience including content, presentation, and teaching methods. Level 2a: modification of attitudes/perceptions: focused on changes in attitudes or perceptions between participant groups toward the intervention. Level 2b: modification of knowledge/skills: for knowledge, focused on the acquisition of concepts, procedures, and principles; for skills, focused on the acquisition of problem solving, psychomotor, and social skills. Level 3: behavioral change: focused on the transfer of learning to the workplace or willingness of learners to apply new knowledge and skills. Level 4a: change in organizational practice: focused on wider changes in the organization or delivery of care attributable to an educational program. Level 4b: focused on improvements in the health and well-being of patients as a direct result of an education initiative.

Similar to more traditional clinical research, education research needs to be performed in a scholarly fashion and shared with a wider audience. In addition to submitting research to gastroenterology journals (e.g., Gastroenterology's Mentoring, Education, and Training Corner), education research can be submitted to education journals such as the Association of American Medical Colleges' Academic Medicine, the Association for the Study of Medical Education's Medical Education, the Accreditation Council for Graduate Medical Education's Journal of Graduate Medical Education, or the European Association for Medical Education in Europe's Medical Teacher; online education warehouses such as MedEdPORTAL (www.mededportal.org) or MERLOT (www.merlot.org); and national conferences as workshops. Also, keep in mind that opportunities arise on a regular basis to share educational videos or images in forums such as the American Society for Gastrointestinal Endoscopy's video journal VideoGIE, The American Journal of Gastroenterology's video of the month, and Clinical Gastroenterology and Hepatology's Images of the Month.

Number 5: Ongoing professional development

Continued Medical Education is a standard requirement to maintain

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an active medical license because it shows ongoing efforts to remain up to date with changes in medicine. Similar opportunities exist with respect to further development as an educator. Given the multitude of manners in which these opportunities can be divided, we have compiled recommendations for resources on educational scholarship based on level of experience and desired level of engagement (Table 1).

Summary

The framework provided should help guide the gastroenterologist on the path of becoming an effective CE in gastroenterology. The success of the future of medical education and our careers requires not only that every CE be productive, but also that each one brings a unique passion to work each day to share. The authors would like to thank all those CEs who contributed to our education, and look forward to learning from you in the future.

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