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GI & HEPATOLOGY NEWS

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A group of internists is alleging that the board is monopolizing the MOC market.

Class-action suit filed against ABIM over MOC

BY ALICIA GALLEGOS
MDedge News

A group of internists is suing the American Board of Internal Medicine over its maintenance of certification (MOC) process, alleging that the board is monopolizing the MOC market.

The lawsuit, filed Dec. 6, 2018, in Pennsylvania district court, claims that ABIM is charging inflated monopoly prices for maintaining certification, that the organization is forcing physicians to purchase MOC, and that ABIM is inducing employers and others to require ABIM certification. The four plaintiff-physicians are asking a judge to find ABIM in violation of federal antitrust law and to bar the board from continuing its MOC process. The suit is filed as a class action on behalf of all internists and subspecialists required by ABIM to purchase MOC to maintain their ABIM certifications. The plaintiffs seek damages and injunctive relief, plus lawsuit and attorney costs arising from ABIM's alleged antitrust violations.

In a statement, ABIM expressed disappointment at the lawsuit and said the organization will vigorously defend itself, adding that doing so will "consume resources far better dedicated to continuous improvement of its programs."

ABIM declined to answer

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AGA Guideline: Treatment of mild to moderate ulcerative colitis

BY AMY KARON
MDedge News

For patients with extensive mild to moderate ulcerative colitis, numerous randomized controlled trials support the use of either standard-dose mesalamine (2-3 grams per day) or diazo-bonded 5-aminosalicylic acid (ASA) instead of low-dose mesalamine, sulfasalazine, or no therapy, state a new guideline from the American Gastroenterological Association, published in Gastroenterology.

Sulfasalazine (2-4 grams per day) is less likely to be tolerated but remains a "reasonable option" for remitted patients who are already on it and for patients with prominent arthritis symptoms, especially if alternative treatments are cost prohibitive, wrote Cynthia W. Ko, MD, MS, of the University of Washington, Seattle, and her associates.

According to the guideline, patients with mild to moderate ulcerative colitis have less than four to six bowel movements per day, only mild or moderate rectal bleeding, no constitutional symptoms, and no high overall inflammatory burden or signs of high inflammatory activity on the Mayo Clinic score and Truelove and Witt's criteria. These patients usually do not require colectomy,

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INSIDE

Aspirin, omega-3 PUFA fail to reduce ADR in high-risk patients

BY ANDREW D. BOWSER
MDedge News

Taking aspirin or an omega-3 polyunsaturated fatty acid daily did not reduce the colorectal adenoma detection rate among high-risk patients in a randomized, placebo-controlled trial, though both drugs showed potential chemopreventive effects.

There was no evidence that aspirin, eicosapentaenoic acid (EPA), or the two agents combined had any effect on the adenoma detection rate, reported Mark A. Hull, PhD, of the

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LETTER FROM THE EDITOR: The shutdown has shut down some science

DR. ALLEN

I read a lot about the inner workings of the pharmaceutical industry and cannot fathom how such prices are justified. Perhaps we physicians and our medical societies should consider raising our voices for our patients.

As I write this editorial, we are within the longest federal government shutdown in our nation's history, a federal judge in Texas has ruled the Affordable Care Act unconstitutional, and there is a class-action suit against the American Board of Internal Medicine (ABIM) regarding maintenance of certification. Being a doctor, these days, is neither easy nor relaxing.

The government shutdown is cheered by some, but it has real consequences for 800,000 government workers who are not getting paid, and our scientific community, where grant applications, hiring, data collection, and other critical roles of government are needed, is at a standstill. The class-action suit against ABIM is the latest action of physicians telling the ABIM that enough is enough. Read more and form your opinion from our page 1 article. The ACA continues to be attacked in a variety of ways. To those who want to abolish it, please have a reasonable alternative in place so that real people with real diseases are not left in a desperate situation.

Drug prices continue to make news. The most recent example is the enormous increase in the cost of insulin. I read a lot about the inner workings of the pharmaceutical industry and cannot fathom how such prices are justified. Perhaps we physicians and our medical societies should consider raising our voices for our patients.

In this month's issue there are several articles about polyp detection and the long-term protective effect of colonoscopy. We are doing really important and excellent work to reduce the burden of colon cancer.

As a heads up, Digestive Disease Week® (DDW) returns to San Diego this year. Housing choices are opening up and in San Diego fill rapidly; visit www.DDW.org/registration for more information. This year's science is groundbreaking and will continue to advance our knowledge about IBD, the microbiome, and other important topics.

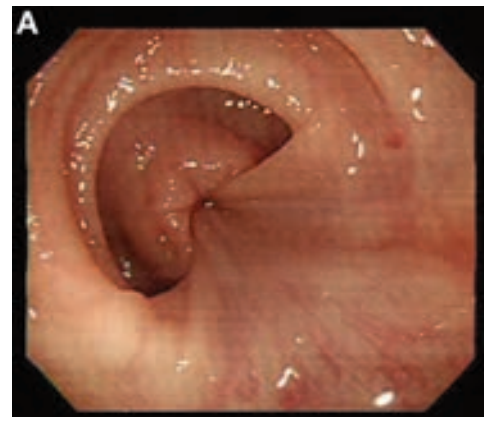
John I. Allen, MD, MBA, AGAF
Editor in Chief

CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

By Yang-Yuan Chen, MD, Cheng-Che Chen, and Chia-Yu Chen. Published previously in Gastroenterology (2017;152[1]:34-5).

An 85-year-old woman presented with a 5-month history of bowel habit change and bloody stool. Initially, she visited a local hospital for help. Her symptoms were intermittent attacks, were relieved with medication, and had increased in severity in the last month. She had developed nausea and anorexia without vomiting. She also noted a 15-kg reduction in body weight over the last 5 months. She visited the outpatient department for further examination through colonoscopy, the results of which showed luminal obstruction with distal fold invagination to the proximal area in the descending colon (Figure A).



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FROM THE AGA JOURNALS

Childhood IBD linked to increased mortality

BY AMY KARON
MDedge News

Children who developed inflammatory bowel disease before the age of 18 had a three- to fivefold increase in risk of death, compared with others in a large, retrospective registry study.

The study, which spanned a recent 50-year period, found "no evidence that [these] hazard ratios have changed since the introduction of immunomodulators and biologics," wrote Ola Olén, MD, PhD, of Karolinska University Hospital in Sola, Sweden, together with her associates. Malignancy was the most frequent cause of death among patients with childhood-onset inflammatory bowel disease, followed by digestive diseases and infections. Absolute numbers of premature deaths were low, but the increase in relative risk was highest among patients with childhood-onset ulcerative colitis with primary sclerosing cholangitis and patients who had a first-degree relative with ulcerative colitis. The findings were published in the February issue of Gastroenterology.

Inflammatory bowel disease is thought to be more severe when it begins in childhood, but data on mortality for these patients are lacking. Using national Swedish health registries, Dr. Olén and her associates compared deaths among 9,442 children and adolescents with inflammatory bowel disease with those among 93,180 others matched by sex, age, and place of residence. Both groups were typically followed through age 30 years, and the study covered 1964 through 2014.

In all, there were 294 deaths among patients with childhood-onset inflammatory bowel disease (2.1 deaths per 1,000 person-years) and 940 deaths among matched individuals (0.7 deaths per 1,000 person-years), for a statistically significant adjusted hazard ratio of 3.2 (95% confidence interval, 2.8-3.7). For every 694 patients with childhood-onset inflammatory bowel disease who were followed through adulthood, there was one additional death per year, compared with a demographically similar population, the researchers determined.

Childhood-onset inflammatory bowel disease was associated with a 2.2-year shorter life expectancy in patients followed through age 65 years, they reported. Thus, a diagnosis of childhood-onset inflammatory bowel disease merits careful follow-up.

Among the 294 deaths, 133 were because of cancer. Consequently, individuals with childhood-onset inflammatory bowel disease had a more than sixfold greater risk of dying from cancer than the general population (HR, 6.6; 95% CI, 5.3-8.2). The risk of death from malignancy was higher among individuals with ulcerative colitis (HR, 9.7) than among those with Crohn's disease (HR, 3.1). Deaths from conditions of the digestive system were next most common, and these included deaths from liver failure.

In all, 27 individuals with childhood-onset inflammatory bowel disease died before their 18th birthday, for a fivefold increase in the adjusted hazard of death, compared with the general population of children and adolescents (HR, 4.9; 95% CI, 3.0-7.7). There was no significant trend in hazard of death according to calendar period, either among children and adolescents, or young adults (followed through age 25 years), the researchers said.

Additionally, childhood-onset inflammatory bowel disease was associated with a 2.2-year shorter life expectancy in patients followed through age 65 years, they reported. Thus, a diagnosis of childhood-onset inflammatory bowel disease merits careful follow-up, especially if patients have ulcerative colitis and primary sclerosing cholangitis, which was the strongest correlate of fatal intestinal cancer in this study.

Funders included the Swedish Medical Society, the Swedish Cancer Society, the Swedish Research Council, the Swedish Foundation for Strategic Research, Magtarmfonden, the Jane and Dan Olsson Foundation, the Mjölkdroppen Foundation, and the Karolinska Institutet Foundation. Dr. Olén disclosed investigator-initiated grants from Janssen and Pfizer. Other investigators also disclosed ties to Janssen, Pfizer, AstraZeneca, Ferring, Celgene, and Takeda.

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SOURCE: Olén O et al. Gastroenterology. 2018 Oct 17. doi: 10.1053/j.gastro.2018.10.028.

Dietary aluminum may trigger IBS

BY WILL PASS
MDedge News

Aluminum ingested in small amounts causes visceral hypersensitivity in rats, suggesting that dietary levels of aluminum may trigger irritable bowel syndrome (IBS) in humans, according to a study published in Cellular and Molecular Gastroenterology and Hepatology.

Rats given oral aluminum exhibited dose-dependent visceral pain along with activation of proteinase-activated receptor-2 (PAR2) and mast cell degranulation, a combination of events that mirror clinical signs and molecular mechanisms of IBS in humans, reported lead author, Nicolas Esquerre, PhD, of Lille Inflammation Research International Center at Université Lille (France), and his colleagues. The study contributes to ongoing research surrounding causes and mechanisms of IBS. These findings suggest that some patients with IBS may benefit from dietary aluminum restriction or chelation therapy.

"[T]he question of the initial trigger [of IBS] still remains unresolved," the investigators wrote. "A more precise link between food and IBS has been demonstrated for gluten and other wheat proteins, lactose, and nickel, highlighting particular subsets of IBS patients now diagnosed as nonceliac gluten/wheat sensitivity, lactose intolerance, and nickel-allergic contact mucositis," they added. "Here, we evaluated the effect of aluminum, a common contaminant of food and water, on abdominal pain."

Aluminum may enter the diet as a food additive, or it may contaminate foods grown in aluminum-rich soil. Other sources of oral exposure include packaging and kitchenware. A previous study showed that most Americans ingest 0.01-1.4 mg/kg of aluminum daily, and 5% ingest 1.58 mg/kg daily (i.e., 95 mg per day for a 60-kg person).

Based on these statistics, rats in the present study received oral aluminum citrate (AlCi) corresponding with three doses of aluminum: 0.5 mg/kg, 1.5 mg/kg, or 3.0 mg/kg. Treatment continued for 30 days, with colorectal distension (CRD) measured on days 2, 4, 8, 15, and 30.

Results showed a dose-dependent relationship between aluminum ingestion and visceral hypersensitivity. Within 2 days, rats receiving 3.0 mg/kg of aluminum exhibited a significantly lower pain threshold, and within 8 days, rats receiving 0.5 mg/kg and 1.5 mg/kg also showed increased visceral hypersensitivity.

After 1 month of treatment, rats receiving 1.5 mg/kg per day demonstrated a 30% increase in pain compared with control animals. In the same group, visceral hypersensitivity began to wane 7 days after cessation of treatment; 4 more weeks were needed to return to baseline. When treatment was restarted, visceral hypersensitivity occurred within 2 days, compared with 8 days upon initial administration. These findings are particularly relevant to some people, as the 1.5-mg/kg dose corresponds with the daily amount of aluminum ingested by 5% of Americans. Similar patterns of response and sensitization were observed in rats ingesting 0.5 mg/kg and 3.0 mg/kg. Female rats were more sensitive to aluminum than were male rats, a sex pattern that mimics human IBS.

Further testing showed that rats treated with zinc citrate (ZnCi) did not exhibit changes to pain threshold, thereby excluding citrate as an aggravating factor. Rat models of noninflammatory and inflammatory colonic hypersensitivity (butyrate enema or intrathecal injection of 25%-50% ethanol in combination with 2,4,6-trinitrobenzenesulfonic acid, respectively) had visceral hypersensitivity similar to that of rats in the 1.5-mg/kg AlCi group.

Testing of colonic tissue from AlCi-treated rats did not reveal inflam-

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matory changes according to a variety of qualifiers, including histology, myeloperoxidase activity, mRNA expression of several inflammatory cytokines, or infiltration of eosinophils or macrophages. Noninflammatory effects of aluminum, however, were found. For instance, treated rats had lower serotonin levels in enteroendocrine cells.

"Enteroendocrine cells are specialized epithelial cells that respond to luminal stimuli by releasing various biologically active compounds," the investigators wrote. "They regulate several physiological and homeostatic functions of the gastrointestinal tract, such as postprandial secretion, motility, immune responses, and sensory functions. A reduced number of enteroendocrine cells has been observed in the duodenum, ileum, and colon of some patients with IBS."

In addition to changes in enteroendocrine cells, AlCi-treated rats had greater colonic mast cell degranulation and histamine with upregulation of histidine decarboxylase transcripts, suggesting that aluminum activated mast cells.

To determine the role of mast cell activation in visceral hypersensitivity, researchers gave rats AlCi with cromoglycate, an inhibitor of mast cell degranulation. This treatment reduced mast cell degranulation and visceral pain threshold, compared with AlCi-treated rats not receiving cromoglycate, suggesting that mast cell degranulation is a primary driver of visceral hypersensitivity. This observation was confirmed by a mast cell–deficient mouse strain (Kit W-sh/W-sh) that had a normal number of mast cells incapable of degranulation. Treating the mast cell–deficient mice with AlCi did not induce visceral hypersensitivity, thereby confirming the role of mast cell degranulation.

Along with mast cell degranulation, AlCi treatment led to PAR2 activation. Investigators explored the significance of this finding with PAR2 knockout mice. When treated with AlCi, PAR2 knockout mice showed no increase in visceral hypersensitivity, suggesting that hypersensitivity is dependent on PAR2 activation. Further testing revealed that mast cell–deficient mice (Kit W-sh/W-sh) did not have PAR2 upregulation either, connecting a sequence in which aluminum triggers mast cell degranulation, which drives PAR2 upregulation, and PAR2 upregulation causes visceral hypersensitivity. The latter two events in this chain – mast cell degranulation and PAR2 upregulation – mirror molecular mechanisms of IBS in humans.

"We speculate that aluminum activates mast cells to release mediators that can increase excitability of nociceptive afferences contributing to the visceral pain phenotype," the investigators wrote. "Taken together, our results linked aluminum to several mechanisms implicated in IBS pathophysiology, highlighting a possible role for aluminum as a triggering factor in IBS development."

The investigators suggested that these findings could influence preventive or therapeutic strategies: "Aluminum might be the first identified dietary risk factor for IBS, implying that measures to limit aluminum dietary consumption or to chelate aluminum may represent novel pathways of prevention and treatment of IBS in some susceptible patients," they wrote.

The study was funded by the European Fund for Regional Economic Development; the Hauts de France Region, Ministère de l'Enseignement Supérieur et de la Recherche (CPER IRENI); and Digestscience (European Research Foundation on Intestinal Diseases and Nutrition).

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SOURCE: Esquerre N et al. Cell Mol Gastroenterol Hepatol. 2019 Sep 20. doi: 10.1016/j.jcmgh.2018.09.012.

Irritable bowel syndrome is a chronic functional gastrointestinal disorder, characterized by relapsing/remitting diarrhea, constipation, and visceral pain. IBS afflicts 10%-25% of the population in developed countries. Despite histologically normal intestinal biopsy specimens, biological signatures of IBS include alterations in intestinal gene expression, increased gut permeability, and changes in gut microbiota composition. Thus, although the cause or causes of IBS are not defined, these and other data highlight the enormous breadth of factors that might play a role in this disorder.

DR. GEWIRTZ

Similar alterations also are associated with inflammatory bowel disease (IBD), although the magnitude of changes is typically greater in IBD. Nevertheless, these data suggest that IBS and IBD may share triggers and pathogenetic mechanisms. That prevalence of both IBS and IBD have shown marked increases in incidence, roughly paralleling the modernization of society that accelerated in the mid-20th century, raises the possibility that environmental factors associated with human activity may be a driver of both diseases. Recent findings suggest that aluminum may be one such trigger. While humans have always been exposed to aluminum, the most abundant metal on earth, industrialization has increased the magnitude of exposure owing to the use of aluminum salts as stabilizers in processed foods and the concentration of groundwater aluminum in agricultural products. Mimicking estimated average human ingestion of aluminum via administering it orally to rats increases their perception of visceral pain.

These results suggest a possible role for increased exposure to aluminum in driving the post–mid 20th century increased incidence of IBS. Unfortunately, only broad societal estimates of aluminum exposure are available, and aluminum levels are difficult to measure in individuals, making it difficult to epidemiologically investigate the role of aluminum in promoting GI disease in humans. Hence, I submit that levels of aluminum ingestion by humans should be more closely monitored and the potential of aluminum to promote GI disease carefully scrutinized.

Andrew Ted Gewirtz, PhD, is distinguished university center professor, Georgia State University's Institute for Biomedical Sciences' Center for Inflammation, Immunity and Infection, Atlanta. He has no conflicts.

Study supports swallowed topical steroids as maintenance for eosinophilic esophagitis

BY AMY KARON
MDedge News

For adults with eosinophilic esophagitis, maintenance treatment with swallowed topical steroids was associated with significantly higher remission rates when compared with "steroid holidays" in a single-center retrospective observational study presented in the February issue of Clinical Gastroenterology and Hepatology.

At a median follow-up time of 5 years, the rate of complete (including clinical, endoscopic, and histologic) remission was 16.1% when patients were receiving swallowed topical steroids but only 1.3% when they were not on these or other maintenance therapies (that is, on "drug holidays"), reported Thomas Greuter, MD, of University Hospital Zürich and the Mayo Clinic in Rochester, Minn., and his associates. Swallowed topical steroids also were associated with significantly higher rates of each individual endpoint (*P* less than .001). Swallowed topical steroid therapy did not appear to cause dysplasia or mucosal atrophy, although esophageal candidiasis was confirmed in 2.7% of visits when patients were on treatment. "Given the good safety profile of low-dose swallowed topical steroid therapy, we advocate for prolonged treatment. Dose-finding trials are needed to achieve higher remission rates," the investigators wrote in Clinical Gastroenterology and Hepatology.

Several studies have confirmed the efficacy of short-term swallowed topical steroids for treating eosinophilic esophagitis, but only one small randomized trial has evaluated longer-term treatment, and participants were followed

Continued on following page

Studies support vedolizumab-calcineurin inhibitor combos but not accelerated infliximab therapy for refractory UC

BY AMY KARON
MDedge News

For patients with treatment-refractory ulcerative colitis, accelerated induction with infliximab did not appear to reduce the need for colectomy, while adding a calcineurin inhibitor to vedolizumab safely and effectively induced clinical remission in nearly half of patients, according to the results of two studies published in the February issue of Clinical Gastroenterology and Hepatology.

The first study retrospectively evaluated 213 patients with acute severe ulcerative colitis who received infliximab rescue therapy at three gastroenterology centers between 2005 and 2017. Rates of subsequent colectomy were similar whether patients received infliximab (5 mg/kg) at weeks 0, 2, and 6, or were on an accelerated schedule (8% vs. 9%, respectively; adjusted odds ratio, 1.35; 95% confidence interval, 0.38-4.82).

However, among patients who received accelerated treatment, those who received a higher initial dose of infliximab (10 mg/kg) were less likely to subsequently undergo colectomy than those who started at 5 mg/kg and received "chaser" 5-mg or 10-mg doses before week 2, reported Niharika Nalagatla, MD, of Massachusetts General Hospital in Boston, with her associates. "While there was no statistically significant difference [between these groups], there were numerically lower rates of in-hospital and long-term colectomy in the 10 mg/kg group, with a trend toward statistical significance at 2 years [OR, 0.44; 95% CI, 0.18-1.12; *P* = .08]," they added.

They reported similar results from their systematic review and meta-analysis of seven studies of infliximab induction schedules in patients with acute severe ulcerative colitis. Accordingly, they called for prospective studies to identify which patients are most likely to benefit from accelerated infliximab therapy.

The second study, which was prospective, included 11 patients with treatment-refractory ulcerative colitis who initially received vedolizumab immunotherapy and then started on a calcineurin inhibitor (either tacrolimus or cyclosporine) during their first 12 months of treatment. Rates of steroid-free clinical remission (Harvey-Bradshaw index score less than 4 or short clinical colitis activity index score less than 2) were 55% at week 14 and 45% at week 52, reported Britt Christensen, MD, of the University of Chicago and the Royal Melbourne Hospital, with her associates.

Two of these patients were hospitalized for intravenous cyclosporine plus corticosteroid therapy because they failed to respond to 3 months of treatment with vedolizumab plus prednisolone (40 mg), the investigators noted. One patient did not respond and ultimately underwent colectomy, while the other tapered off cyclosporine after 51 days of treatment and remained in steroid-and calcineurin-free clinical remission at 12 months.

Serious adverse events were uncommon, reflecting the relatively good safety profile of vedolizumab. Combination anti–tumor necrosis factor and calcineurin inhibitor therapy has been linked to severe infections and deaths, and clinical trials of vedolizumab ex-

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We physicians are not known for our humility. However, acute severe ulcerative colitis (UC) can humble even the most confident inflammatory bowel disease specialist. The study by Nalagatla et al. did not show a difference of colectomy outcomes between accelerated versus standard infliximab induction. However, as the authors point out, their methodology was unable to address confounding by severity. Review of the baseline characteristics implies presence of confounding with numerically higher markers of inflammation in the accelerated infliximab group. The signal of lower, although not statistically significant, odds of colectomy in subgroup analyses of 10 mg/kg versus standard induction should encourage further investigation in 10-mg/kg induction dosing for acute severe UC.


DR. HOU

Christensen et al. described the novel use of coinduction of combination calcineurin inhibitors with vedolizumab in 11 UC patients, observing calcineurin inhibitor–free remission in 45% at week 52. Adverse events occurred as would be expected in severe UC; however, no additional major safety signals were observed with combination therapy. One should consider that the study was performed at a facility with standardized protocols and great experience in calcineurin inhibitors – prior studies at facilities with less experience have resulted in significant morbidity with calcineurin inhibitor monotherapy in this population. While this study is too small to change clinical practice, it highlights the opportunity to further study combination therapy of vedolizumab with calcineurin inhibitors or other more accessible immunosuppressive agents, such as tumor necrosis factor antagonists or tofacitinib in this population.

These two studies continue to expand possibilities to manage acute severe UC and direct areas to focus future research.

Jason Ken Hou, MD, MS, is assistant professor of medicine-gastroenterology, director of the GI & Hepatology Fellowship Program, and director of research–IBD at Baylor College of Medicine, Houston, and staff physician of gastroenterology at Michael E. DeBakey VA Medical Center, Houston. He has financial ties to Janssen, AbbVie, and Pfizer.

Continued from previous page

for only 1 year. Dr. Greuter and his associates therefore analyzed retrospective data from 229 adults in Switzerland who received swallowed topical steroids for eosinophilic esophagitis between 2000 and 2014. Induction therapy consisted of 1 mg swallowed topical steroids twice daily, allowing 2-4 weeks for a clinical response. Patients then received infinite maintenance therapy with 0.25 mg swallowed topical steroids twice daily. Patients tended to be male and diagnosed in their late 30s. Endoscopy commonly showed corrugated rings, white exudates, edema, and furrows, and 35% of patients had strictures. Peak eosinophil count typically was 25 cells per high-power frame.

Among 819 follow-up visits, 336 (41%) occurred when patients were on maintenance swallowed topical steroid therapy. The median duration of maintenance therapy prior to a follow-up visit was 347 days (interquartile range, 90-750 days) or 677 doses (IQR, 280-1,413 doses). The rate of clinical remission was 31% when patients were on maintenance treatment but only 4.5% when they were not (*P* less than .001). Respective rates of endoscopic and histologic remission were 48.8% versus 17.8% (*P* less than .001) and 44.8% versus 10.1% (*P* less than .001). After numerous demographic and clinical variables were taken into account, the only significant predictors of clinical remission were treatment with swallowed topical steroids (odds ratio, 16.98; 95% confidence interval, 6.69-43.09) and a negative family history of esophageal eosinophilia (OR, 4.02; 95% CI, 1.41-11.47).

This study excluded patients whose eosinophilic esophagitis had responded to proton pump inhibitor therapy. Also, the maintenance dose of swallowed topical steroid (0.25 mg twice daily) probably was too low to achieve efficacious drug levels in the esophageal mucosa, which could explain the high proportion of treatment-refractory cases, according to the researchers. Evaluating a higher maintenance dose "would be of particular interest in the future," they added.

The Swiss National Science Foundation provided partial funding. Dr. Greuter disclosed a travel grant from Falk Pharma GmbH and Vifor and an unrestricted research grant from Novartis.

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FROM THE AGA JOURNALS

Metachronous advanced neoplasia linked to diminutive polyp number, not histology

BY AMY KARON
MDedge News

Among patients with diminutive (1-5 mm) colonic polyps, multiplicity was a significant risk factor for advanced metachronous colonic neoplasia, while advanced histologic features alone were not, according to the results of a pooled analysis of data from 64,344 patients.

Metachronous advanced neoplasia affected similar proportions of patients with and without high-risk diminutive polyps (17.6% vs. 14.6%, respectively; relative risk, 1.13; 95% confidence interval, 0.79-1.61), reported Jasper L.A. Vleugels, MD, of the University of Amsterdam, together with his associates. However, patients with at least three nonadvanced (diminutive or small) adenomas were at significantly increased risk of metachronous advanced neoplasia, compared with low-risk patients (overall risk ratio, 2.12; 95% CI, 1.89-2.38), the investigators wrote in the February issue of Gastroenterology.

This multicenter study spanned 12 prospectively evaluated cohorts of patients in the United States and Europe. All patients underwent colonoscopy because of a positive fecal immunochemical test result or for the purpose of screening, surveillance, or evaluation of symptoms. The researchers defined low-risk patients as individuals with one or two diminutive or small nonadvanced adenomas. In contrast, "high-risk" patients had a polyp with advanced histology (at least a 25% villous component, high-grade dysplasia, or colonic rectal carcinoma), at least three diminutive (1-5 mm) or small (6-9 mm) nonadvanced adenomas, or an adenomatous or sessile serrated lesion measuring at least 10 mm.

Among more than 50,000 diminutive polyps in the dataset, the prevalence of advanced histologic features was 7.1% among patients who underwent colonoscopy because of a positive fecal immunochemical test and 1.5% among those who had a colonoscopy for other reasons (P = .04). However, statistically similar proportions of patients in each of these subgroups were classified as "high risk" because of advanced histology (0.8% and 0.4%, respectively) or multiplicity (3.8% and 3.0%, respectively). Because metachronous advanced neoplasia was detected in similar proportions of patients with and without diminutive polyps with advanced histologic features (17.6% vs. 14.6%, respectively), the presence of such features did not independently predict metachronous advanced neoplasia, either overall (relative risk, 1.13; 95% CI, 0.79-1.61), or in either subgroup.

"On the other hand, multiplicity of diminutive adenomas was associated with increased risk of metachronous advanced neoplasia," the researchers wrote. Among these patients, nearly 24% of those in the fecal immunochemical subgroup developed metachronous advanced neoplasia, as did nearly 30% of those who had a colonoscopy for other reasons, yielding risk ratios of 2.45 (95% CI, 1.67-3.58) and 1.92 (95% CI, 1.68-2.20), respectively.

"While multiplicity has been described as a risk factor of metachronous advanced adenomas, we were surprised to find that even if all adenomas are diminutive, the risk was increased," the investigators commented. Taken together, the findings "underline the importance of correctly classifying diminutive adenomatous lesions, preventing misclassification of patients with at least three adenomas to a low-risk status."

Partial funding for this study came from PERIS and Fundción Científica de la Asociación Española contra el Cáncer. Dr. Vleugels reported having no conflicts of interest. Three coinvestigators disclosed ties to Fujifilm, Olympus, Norgine, Clinical Genomics, and Boston Scientific.

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SOURCE: Vleugels JLA et al. Gastroenterology. 2018 Nov 2. doi: 10.1053/j.gastro.2018.10.050.

When to perform surveillance colonoscopy in patients previously diagnosed with colorectal neoplasms is one of the most significant questions facing experts creating guidelines for colorectal cancer (CRC) screening. This study by Vleugels et al. provides important information that should better inform this issue.


DR. NESS

The authors pooled data from 12 different study cohorts of patients undergoing colonoscopy in either the United States or Europe. The cohorts included patients who underwent colonoscopy to follow up a positive fecal immunochemical test (FIT) or as a primary test for screening, surveillance, or symptom management. The authors found that diminutive adenomas (1-5 mm) rarely contained advanced histology (CRC, high-grade dysplasia, or more than 25% villous features) and that these lesions seldom defined patients regarding risk for metachronous neoplasms. They also found that high-risk patients defined by 1-2 diminutive adenomas with advanced histology were no more likely to develop metachronous advanced neoplasia (adenoma containing advanced histology, at least three diminutive or small nonadvanced adenomas, or an adenoma or sessile serrated lesion at least 10 mm) than were patients defined as low risk by their initial adenoma histology.

Interestingly, multiplicity (more than three) of diminutive or small adenomas regardless of histology did predict a significantly increased risk of metachronous advanced neoplasia. These data support a resect-and-discard strategy (not sending the resected polyp to pathology) for diminutive polyps and polyp surveillance guidelines that employ less frequent colonoscopy to follow patients whose most significant finding at initial colonoscopy is a diminutive adenoma.

Future studies should examine the risk for metachronous neoplasms posed by diminutive adenoma within the milieu of other patient characteristics informing colorectal cancer risk.

Reid M. Ness, MD, MPH, AGAF, is an associate professor of medicine in the division compliance and a quality expert in the division of gastroenterology, hepatology, and nutrition in the department of medicine at Vanderbilt University Medical Center, Nashville, Tenn. He has no financial conflicts to disclose.

Continued from page 9

cluded patients with calcineurin inhibitor exposure. However, vedolizumab primarily targets the localized immune system of the gut, so adding an agent "with broad immune-suppressing effects would not [lead to greater] infective and other complications," the investigators wrote. "Indeed, no significant toxicity was observed in our series, despite the fact that many patients were on quadruple immunosuppressive therapy, at least initially."

Dr. Nalagatla reported receiving support from the National Institutes of Health and the Crohn's & Colitis Foundation. She reported having no relevant conflicts of interest. One of her coinvestigators reported ties to AbbVie, Takeda, Gilead, Merck, and Pfizer. Dr. Christensen and her associates reported receiving support from the University of Chicago and the government of Australia. Dr. Christensen reported ties to Janssen, AbbVie, Takeda, and Pfizer, and four of her coinvestigators also reported ties to a number of pharmaceutical companies.

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SOURCES: Nalagatla N et al. Clin Gastroenterol Hepatol. 2018 Jun 23. doi: 10.1016/j.cgh.2018.06.031; Christensen B et al. Clin Gastroenterol Hepatol. 2018 May 8. doi: 10.1016/j.cgh.2018.04.060.

Guideline public comment period framework

AGA is dedicated to integrity and transparency in the development of clinical guidance.

When preparing guidelines, AGA follows the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process and makes draft guidelines available for public comment. In addition, to keep academic integrity of the AGA guideline, clinical practice update, and clinical pathway process, AGA follows the framework outlined by the Council of Medical Specialty Societies (CMSS) in *The Code for Interaction with Companies*.

The Code for Interaction with Companies states:
"7.15. Societies will not permit Guideline development panel members or staff to discuss a Guideline's development with Company employees or representatives, will not accept unpublished data from Companies, and will not permit Companies to review Guidelines in draft form, except if a Society permits public or member comment on draft Guidelines as a part of the Society's published Guideline development process."

The Clinical Guidelines Committee and Clinical Practice Updates Committee strive to keep AGA's clinical practice tools independent of industry influence and remain solely based on scientific evidence. As a result of this effort, AGA's writing panels and chairs will have no direct communication with industry. Companies will have the opportunity to submit feedback during the public comment period. The panel will review any comments submitted through the online platform along with feedback from the public. The writing panel will take these suggestions into consideration when making revisions following the public comment period.

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AGA represents gastroenterology at Core Quality Measures Collaborative

Megan Adams, MD, JD, MSc, is to cochair gastroenterology workgroup with the task of reviewing the gastroenterology core measure set, which is designed for adoption and implementation by private health plans to reduce physician reporting requirements.

The Centers for Medicare & Medicaid Services (CMS) and America's Health Insurance Plans (AHIP) – in partnership with the National Quality Forum (NQF) – have officially formalized the Core Quality Measures Collaborative (CQMC) to improve health care quality for every American.

Dr. Adams, chair of AGA's Quality Measures Committee, has been appointed as a cochair of the CQMC Gastroenterology workgroup. The workgroup is tasked with reviewing and making recommendations for a revised, updated gastroenterology core measure set.

The CQMC is a multistakeholder, voluntary effort created to promote measure alignment and harmonization across public and private payers. The collaboration aims to add focus to quality improvement efforts, reduce the burden of reporting for providers, and offer consumers actionable information to help them make decisions about where to receive their care.

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Help spark scientific breakthroughs with the AGA Research Foundation

The way we diagnose and treat patients now is the result of years of research. But securing the future of the field is no small task. Promising early-stage investigators find it increasingly difficult to secure funding, and many leave the field because they are unable to sustain a research career.


DR. HUH

A donation to the charitable arm of the AGA, the AGA Research Foundation, will help fill the funding gap and contribute to this tradition of discovery.

The foundation provides a key source of funding at a critical juncture in a young investigator's career.

Help spark the scientific breakthroughs of today, so clinicians will have the tools to improve care tomorrow. Your tax-deductible donation will make a critical difference in retaining talented GI scientists, like Won Jae Huh, MD, whose research will impact the future care of patients.

"This funding mechanism will secure my research time to investigate signaling pathways involved in the pathogenesis of Ménétrier's disease, and will provide resources and support to launch my research career. The results from my research project will be helpful for treating Ménétrier's disease patients."

Make a gift today. An outright gift will help fund the AGA Research Awards Program. Your gift will assist in furthering basic digestive disease research, which can ultimately advance research into all digestive diseases. The financial benefits include an income tax deduction and possible elimination of capital gains tax.

Donate on the foundation's website at www.gastro.org/donate online or by mail to 4930 Del Ray Avenue, Bethesda, MD 20814-2512.

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2018 AGA legislative wins

To those who took time to advocate on behalf of your profession and patients, thank you. Because of your efforts, we achieved several key successes that benefit clinicians, researchers and patients.

Together we were able to help advance several AGA policy priorities – administrative burden relief, digestive disease research and funding, and patient access and protection – as well as the science and practice of gastroenterology.

This year, we will be counting on you, our members, to again lead the charge to achieve AGA's mission – empowering clinicians and researchers to improve digestive health – by calling on legislators and regulators to ensure the voice of gastroenterology continue to be heard.

NIH funding increase

AGA advocated and secured a $2 billion increase in NIH funding for fiscal year (FY) 2019. When added to increases from the two previous fiscal years, NIH's funding has increased by 30 percent over the past three years, which is the largest increase since the doubling period in the last decade.

IPAB repeal prevents automatic Medicare cuts

Congress repealed the Independent Payment Advisory Board (IPAB) that was created as part of the Affordable Care Act (ACA). AGA and all of organized medicine long opposed IPAB since its sole purpose was to make budgetary cuts to Medicare if it reached a certain threshold of spending.

MIPS changes means more flexibility for physicians

AGA and the physician community were successful in securing flexibility under the new Medicare Quality Payment Program and the Merit-based Incentive Payment System (MIPS) that were created under the Medicare Access and CHIP Reauthorization Act. The changes give CMS more flexibility in implementing the program and will ensure that physicians have an opportunity to be successful in MIPS.

500 AGA members prevent radical changes to outpatient documentation

In response to a CMS proposal to radically change how outpatient evaluation and management (E/M) services are documented, more than 500 AGA members urged CMS not to move forward with its plan. As a result, CMS withdrew or delayed many of the proposed changes to E/M services that negatively impacted reimbursement. CMS did move forward with several changes to E/M documentation in an effort to reduce administrative burden.

AGA members send more than 940 letters to Congress

AGA launched the Congressional Advocates Program to provide an infrastructure and tools for members to effectively advocate on behalf of their profession and patients. AGA members heeded our calls to action and sent more than 940 letters sent to Congress and federal agencies throughout 2018. We thank our advocates whose participation makes a difference.

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AGA supports draft strategic plan for NIH nutrition research

In a comment letter to NIH, AGA applauds the National Institutes of Health (NIH) Nutrition Task Force for releasing a comprehensive and ambitious draft strategic plan for nutrition research that aims to address critical gaps in evidence about nutrition and its influence on human health. Evidence from nutrition studies that are rigorous, reproducible, and transparent will be invaluable to clinicians, who currently struggle to provide meaningful guidance to their patients on nutritional approaches and interventions. NIH coming forward with this strategic plan is an important step forward.

The draft plan acknowledges the significant role of the gut microbiome in mediating the effects of diet on health. AGA recognizes the importance of this issue for AGA and the Center for Gut Microbiome Research and Education, whose mission is to advance research and education on the gut microbiome with the goal of improving human health. AGA supports the plan's emphasis on the role of the microbiome.

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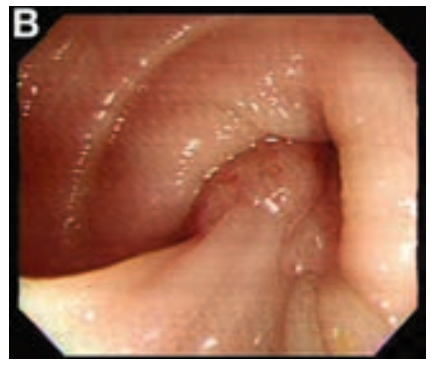
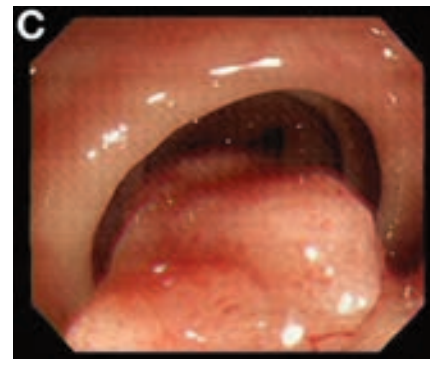
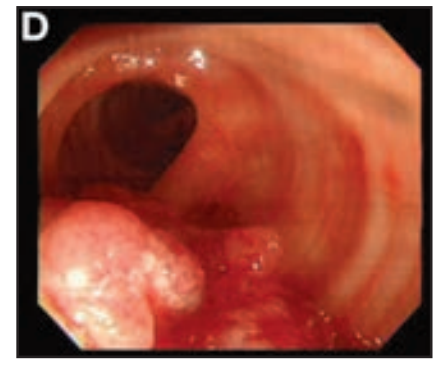
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What is your diagnosis?" on page 6: Retrograde colocolic intussusception induced by colonic adenocarcinoma







AGA Institute

We used biopsy forceps for slow retraction (Figure B) and complete reduction (Figure C). The colonoscope was further inserted up to the cecum and no other lesions were found. A very large polyp was excised partially using a snare for the prevention of repeated intussusception and for histologic examination (Figure D). The pathology revealed adenocarcinoma and the patient underwent surgery. Recovery was uneventful, and the patient was discharged 1 week later.

Intussusception is defined as the invagination of a segment of the bowel and its mesentery into the adjacent bowel lumen. It is a common cause of intestinal obstruction in children, but rare in adults. Adult intussusception accounts for 5% of all causes of bowel obstruction and 5%-10% of all intussusception, and usually has a lead point.[1] Retrograde colocolic intussusception is especially rare, with only 26 cases reported up to 2014.[2] Altered peristalsis in focal areas of the bowel wall can lead to dysrhythmic contractions and cause retrograde intussusception.

Adult colonic intussusception has atypical, nonspecific, intermittent, and vague symptoms and signs, resulting in a diagnostic challenge. Approximately one-half of patients present with symptoms of colonic obstruction with a duration of more than 1 month, as in our case. Many cases involve acute intestinal obstruction and are managed through emergency operation. Ultrasound imaging and computed tomography scans are the most sensitive and most commonly used preoperative diagnostic modalities. Colonoscopy is a useful tool for evaluating intussusception in colocolic intussusception,[3] but there is no reported diagnosis of retrograde colocolic intussusception and reduction, as in this case.

Treatment of adult intussusception is more frequently surgical compared with that in children, and leads to resection of the involved bowel segment without reduction before resection.[3] In our case, intussusception was reduced easily with biopsy forceps under a direct colonoscopic view and was cured through elective laparoscopic left hemicolectomy after histologic proof was obtained.

References

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3. Kamble MA, Thawait AP, Kamble AT. Left side reverse colocolic intussusception secondary to malignant polypoidal growth: a rare clinical entity. Int Surg J. 2014;1:39-42.

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Each worked on one side of colon

Aspirin *from page 1*

Institute of Biomedical and Clinical Sciences at the University of Leeds (England), and his coinvestigators.

However, both agents decreased the mean number of adenomas per participants, and showed subtype- and location-specific reductions in adenomas that were consistent with previous studies, according to the investigators.

"Existing data on colorectal cancer risk reduction by aspirin suggest that the decrease in colorectal adenoma recurrence that we report for both agents is likely to translate into a clinically meaningful decrease in long-term colorectal cancer risk," Dr. Hull and his coauthors said in the report, which appears in the Lancet.

Their randomized, double-blind, multicenter trial, known as the seAFOod Polyp Prevention trial, included participants aged 55-73 years with high-risk adenoma features at screening colonoscopy. A total of 709 participants were enrolled between November 2011 and June 2016.

Adenoma detection rate, the primary endpoint, was 62% overall, and similarly, 63% in the EPA group, 61% in the aspirin group, 61% in the EPA plus aspirin group, and 61% for placebo. There was no evidence that either drug had any effect on this endpoint, according to investigators, who reported risk ratios of 0.98 (95% confidence interval, 0.87-1.12) for EPA and 0.99 (95% CI, 0.87-1.12) for aspirin.

However, aspirin reduced the mean total number of adenomas per participant versus placebo (incidence rate ratio, 0.78; 95% CI, 0.68-0.90), as well as the number of adenomas in the right colon (IRR, 0.73; 95% CI, 0.61-0.88).

While EPA by contrast did not conclusively reduce the mean total number of adenomas per participant, it did reduce the number of adenomas in the left colon, with an IRR of 0.75 (95% CI, 0.60-0.94).

Both aspirin and EPA were generally well tolerated, according to Dr. Hull and his colleagues, though the number of gastrointestinal adverse events was higher in the EPA-alone group, at 146 events, versus 85, 86, and 68 events in the placebo, aspirin, and EPA plus aspirin groups, respectively.

For optimal use of aspirin and EPA for prevention of colorectal adenomas, the approach might need to be tailored to the individual patient.

For optimal use of aspirin and EPA for prevention of colorectal adenomas, the approach might need to be tailored to the individual patient, Dr. Hull and his coauthors wrote.

"A key objective of future work will be to apply precision medicine principles to establish which individuals might gain most from chemoprevention with one or both agents, based on baseline colorectal adenoma characteristics alone or together with other mucosal biomarkers," they added.

Trial funding came from the U.K. Medical Research Council and the National Institute for Health Research. Medicine and placebo were provided without charge by SLA Pharma and Bayer. Dr. Hull provided disclosures related to SLA Pharma, Bayer, and Thetis Pharmaceuticals.

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SOURCE: Hull MA et al. Lancet. 2018 Nov 19. doi: 10.1016/S0140-6736(18)31775-6.

Negative colonoscopy linked with lower risk for more than 10 years

BY BIANCA NOGRADY
MDedge News

A negative colonoscopy result is associated with a reduced risk of colorectal cancer (CRC) for more than 12 years after the examination, compared with an unscreened population, new research has found.

In a retrospective cohort study published in JAMA Internal Medicine, researchers analyzed data from 1,251,318 individuals at average risk of CRC who were eligible to participate in screening over more than 9 million person-years of follow-up.

They found that screened individuals with a negative result had an adjusted 46%-95% lower risk of CRC and 29%-96% lower risk of CRC mortality than unscreened individuals across more than 12 years of follow-up.

At 10 years post colonoscopy, participants who had a negative colonoscopy result still had a significant 46% lower risk of CRC (hazard ratio, 0.54; 95% confidence interval, 0.31-0.94) and 88% lower risk of CRC mortality (HR, 0.12; 95% CI, 0.02-0.82).

Jeffrey K. Lee, MD, of Kaiser Permanente San Francisco, and his coauthors wrote, "The current guideline-recommended 10-year rescreening interval is not based on a predetermined risk threshold, and while we observed a reduced risk of CRC and related deaths throughout the more than 12-year follow-up period, an examination of absolute risk [incidence] could provide another justification for the timing for rescreening.."

"Additional research is needed to evaluate the costs and benefits of earlier versus later rescreening, optimal rescreening tests following a negative colonoscopy result, and whether the benefits of rescreening vary between subgroups."

The study showed that the rate of repeat endoscopic procedures increased at year 10, largely because of screening colonoscopies which are recommended at 10-year intervals. However, in a separate analysis, the authors excluded colonoscopies for a screening indication and still found a similar reduction in the risk of CRC.

The data also showed a 22%-87% lower risk of proximal CRC, a 50%-99% lower risk of distal cancer, a 31%-95% lower risk of early-stage CRC, and a 56%-96% reduced risk of advanced-stage CRC among those who had a negative result, compared with those who did not undergo screening.

The authors wrote that this pattern of greater risk reductions in the distal versus proximal cancer had been seen in previous studies and could be the result of incomplete examinations, inadequate bowel cleansing, challenges in identifying right colon polyps and sessile serrated adenomas, or differences in polyp biology in the proximal versus distal colon.

The incidence rates of CRC among those who had a negative result from colonoscopy ranged from 16.6 per 100,000 person-years (95% CI, 8.2-12.8) at 1 year after screening to 133.2 per 100,000 person-years (95% CI, 70.9-227.8) at 10 years. In comparison, the incidence rates among the unscreened population increased from 62.9 per 100,000 person-years (95% CI, 55.7-70.0) at year 1 to 224.8 per 100,000 person-years (95% CI, 202.5-247.0) after year 12.

Mortality rates from CRC at year 1 were 6.8 per 100,000 person-years (95% CI, 0.8-12.7) in the negative results group and 10.5 (95% CI, 8.2-12.8) in the unscreened cohort. At year 12, that figure was 92.2 per 100,000 person-years (95% CI, 19.0-165.4) in the negative results cohort, while after year 12 in the unscreened cohort, CRC mortality rates increased to 192 per 100,000 person years (95% CI, 7-214.3).

While the study made use of a validated cancer registry to ensure they accurately captured cancers and mortality, the authors acknowledged that they weren't able to adjust for residual confounding factors such as red-meat intake or smoking.

The study was supported by the National Cancer Institute, AGA, and the Sylvia Allison Kaplan Foundation. No conflicts of interest were reported.

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SOURCE: Lee JK et al. JAMA Intern Med. 2018 Dec 17. doi: 10.1001/jamainternmed.2018.5565.

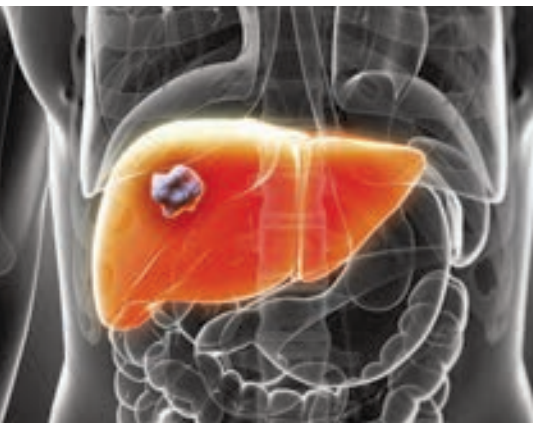
AGA Resource
The AGA GI Patient Center provides education materials that can help your patients better understand their colorectal cancer risk and prepare for a colonoscopy. Visit patient.gastro.org to review and download.

HCC screening linked with improved tumor detection

BY CALEB RANS
MDedge News

Hepatocellular carcinoma (HCC) screening in patients with cirrhosis is an effective early cancer–detection technique that remains underutilized in clinical practice, according to results from a study published in Clinical Gastroenterology and Hepatology.

"Our study's aim was to characterize utilization of HCC screening receipt and its association with early tumor detection and improved survival in a nationally representative cohort of patients in the United States," wrote Debra T. Choi, PhD, MPH, of Baylor College of Medicine, Houston, and her colleagues.



ERAXION/THINKSTOCK

The researchers retrospectively studied a cohort of 13,174 patients with HCC from 2003 to 2013 included in the Surveillance, Epidemiology, and End Results Program–Medicare database. They examined the acquisition of HCC in the 3 years leading up to HCC diagnosis using three separate categories: consistent, inconsistent, or no screening. Dr. Choi and her colleagues studied the associations between receiving HCC screening and subsequent effects on overall survival.

"HCC prognosis depends on tumor stage at the time of diagnosis, with curative treatment options only available for patients diagnosed at an early stage," the researchers wrote. "Patients with early-stage HCC can achieve 5-year survival rates of 70% if they undergo surgical resection or liver transplantation, compared to a median survival of 1 year for patients with advanced HCC," they added.

After multivariable analysis, the investigators found that 51.1% of patients with cirrhosis did not receive screening in the 3 years leading up to HCC diagnosis. In addition, they went on to report that only 6.8% of patients were consistently screened on an annual basis.

In terms of efficacy, consistent screening was associated with an increased rate of early-stage tumor detection (odds ratio, 1.98, 95% confidence interval, 1.68-2.33) and decreased risk of death (hazard ratio, 0.76, 95% CI, 0.70-0.83) after adjustment for lead time bias. Given these results, Dr. Choi and her colleagues said that early HCC screening may help with hepatic tumor detection at later disease stages.

The investigators noted that several patient-specific factors may be driving these associations. In particular, they found a link between female sex and receiving HCC screening. Dr. Choi and her colleagues suggested this association is not related to the perceived benefits from screening.

"Studies have suggested females may be more likely to adhere to screening recommendations; however, patient adherence is not a common barrier to HCC screening completion and therefore it is unclear if this is the sole driver of this association," they acknowledged.

Moving forward, the researchers highlighted the importance of educating primary care providers about the benefits of screening. Moreover, they said that screening receipt is currently on the rise, which has shown positive effects on overall survival.

The Center for Innovations in Quality, Effectiveness, and Safety funded the study. Additional support was provided by the Texas A&M Health Science Center Engineering Experiment Station big data seed grant program. The authors reported no conflicts of interest.

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SOURCE: Choi DT et al. Clin Gastroenterol Hepatol. 2018 Oct 25. doi: 10.1016/j.cgh.2018.10.031.

In Focus
Brought To You By The New Gastroenterologist

New concepts in the management of acute pancreatitis

BY AMAR MANDALIA, MD, AND MATTHEW J. DIMAGNO, MD, AGAF

Dr. Mandalia is a fellow, gastroenterology, department of internal medicine, division of gastroenterology, Michigan Medicine, Ann Arbor; **Dr. DiMagno** is associate professor of medicine, director, comprehensive pancreas program, department of internal medicine, division of gastroenterology, University of Michigan, Ann Arbor. Dr. Mandalia reports no conflicts of interest. Dr. DiMagno received honoraria from BMJ, for podcasts entitled "Pancreatic Disorders" and "Best of DDW" (Digestive Disease Week®), the William M. Steinberg Board Review in Gastroenterology and Best Practices Course for presentations on Acute Pancreatitis and Chronic Pancreatitis/Pancreatic Potpourri, and the American Gastroenterological Association Institute Council for serving as a clinical expert author for the technical review on the initial medical management of acute pancreatitis, received a consulting fee from Cystic Fibrosis Foundation Therapeutics, and serves as an advisory board member of the National Pancreas Foundation Michigan Chapter.

Introduction

Acute pancreatitis (AP) is a major clinical and financial burden in the United States. Several major clinical guidelines provide evidence-based recommendations for the clinical management decisions in AP, including those from the American College of Gastroenterology (ACG; 2013),[1] and the International Association of Pancreatology (IAP; 2013).[2] More recently, the American Gastroenterological Association (AGA) released their own set of guidelines.[3,4] In this update on AP, we review these guidelines and reference recent literature focused on epidemiology, risk factors, etiology, diagnosis, risk stratification, and recent advances in the early medical management of AP. Regarding the latter, we review six treatment interventions (pain management, intravenous fluid resuscitation, feeding, prophylactic antibiotics, probiotics, and timing of endoscopic retrograde cholangiopancreatography (ERCP) in acute biliary pancreatitis) and four preventive interventions (alcohol and smoking cessation, same-admission cholecystectomy for acute biliary pancreatitis, and chemoprevention and fluid administration for post-ERCP pancreatitis [PEP]). Updates on multidisciplinary management of (infected) pancreatic necrosis is beyond the scope of this review. Table 1 summarizes the concepts discussed in this article.

TABLE 1
Recent advances in AP epidemiology, evaluation, and management

Epidemiology, risk factors, and etiology
• Incidence of AP is increasing, but mortality is decreasing
• Alcohol and gallstones remain most common causes of AP
• Smoking is an independent risk factor for AP
• Cannabis is a possible risk factor for toxin-induced AP
• In IBD, AP is typically due to gallstones or medications
• Pancreatic cancer uncommon but established cause of first-attack AP
Evaluation
• Etiologic laboratory testing should include liver panel (ALT ~ 3 × ULN, high PPV for biliary AP), triglycerides, calcium
• Transabdominal ultrasound for all patients with AP to exclude biliary cause
• Cross-sectional imaging overutilized during initial evaluation of AP
• Risk stratification tools have moderate predictive value for severe AP
Fluids
✓ Goal-directed fluid therapy recommended in early treatment of AP
✓ No recommendation for/against normal saline or lactated Ringer's
✓ Advise against use of hydroxyethyl starch
Prophylactic antibiotics/probiotics
✓ Prophylactic antibiotics not recommended for (sterile) necrotizing AP
• Probiotics not recommended for severe AP
Nutrition
✓ Early (<24 hours) oral feeding as tolerated rather than NPO
✓ For inability to feed orally, enteral preferred over parental nutrition
✓ When enteral feeding required (severe or necrotizing) -> NG or nasoenteral is acceptable
ERCP for acute biliary pancreatitis (ABP)
• Urgent ERCP (<24 hours) for ABP complicated by cholangitis
✓ Routine use of urgent ERCP not recommended for ABP
Prevention
✓ Same-admission cholecystectomy for uncomplicated ABP
✓ Same hospitalization brief alcohol intervention for alcohol-induced AP
• Same-admission smoking cessation counseling
• Post-ERCP pancreatitis: rectal indomethacin, periprocedural fluid therapy, prophylactic ductal stenting. Combo therapy requires further studies

✓ Focus of 2018 AGA guideline and technical review

Recent advances in epidemiology and evaluation of AP

Epidemiology

AP is the third most common cause of gastrointestinal-related hospitalizations and fourth most common cause of readmission in 2014.[5] Recent epidemiologic studies show conflicting trends for the incidence of AP, both increasing[6] and decreasing,[7] likely attributable to significant differences in study designs. Importantly, multiple studies have demonstrated that hospital length of stay, costs, and mortality have declined since 2009.[6,8-10]

Persistent organ failure (POF), defined as organ failure lasting more than 48 hours, is the major cause of death in AP. POF, if only a single organ during AP, is associated with 27%-36% mortality; if it is multiorgan, it is associated with 47% mortality.[1,11] Other factors associated with increased hospital mortality include infected pancreatic necrosis,[12-14] diabetes mellitus,[15] hospital-acquired infection,[16] advanced age (70 years and older),[17] and obesity.[18] Predictive factors of 1-year mortality include readmission within 30 days, higher Charlson Comorbidity Index, and longer hospitalization.[19]

Risk factors

We briefly highlight recent insights into risk factors for AP (Table 1) and refer to a recent review for further discussion.[20] Current and former tobacco use are independent risk factors for AP.[21] The dose-response relationship of alcohol to the risk of pancreatitis is complex,[22] but five standard drinks per day for 5 years is a commonly used cutoff.[1,23] New evidence suggests that the relationship between the dose of alcohol and risk of AP differs by sex, linearly in men but nonlinearly (J-shaped) in women.[24] Risk of AP in women was decreased with alcohol consumption of up to 40 g/day (one standard drink contains 14 g of alcohol) and increased above this amount. Cannabis is a possible risk factor for toxin-induced AP and abstinence appears to abolish risk of recurrent attacks.[25]

Patients with inflammatory bowel disease (IBD) have a 2.9-fold higher risk for AP versus non-IBD cohorts[26] with the most common etiologies are from gallstones and medications.[27]

In patients with end-stage renal disease (ESRD), the risk of AP is higher in those who receive peritoneal dialysis, compared with hemodialysis[28-33] and who are women, older, or have cholelithiasis or liver disease.[34]

As recently reviewed,[35] pancreatic cancer appears to be associated with first-attack pancreatitis with few exceptions.[36] In this setting, the overall incidence of pancreatic cancer is low (1.5%). The risk is greatest within the first year of the attack of AP, negligible below age 40 years but steadily rising through the fifth to eighth decades.[37] Pan-

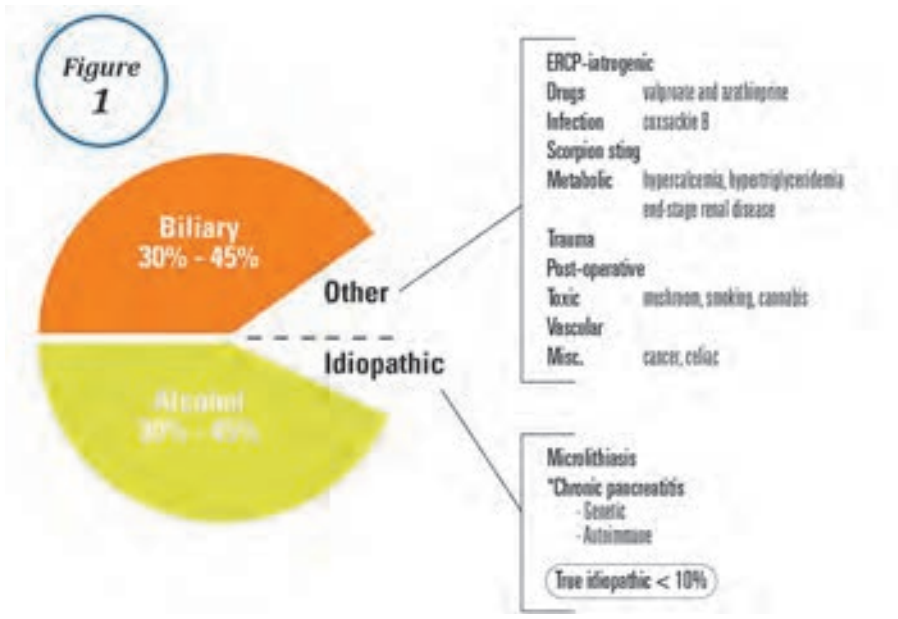

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Figure 1. Etiology and risk factors of acute pancreatitis are outlined.

*Patients with chronic pancreatitis may initially present with a first attack of pancreatitis and be misclassified as having acute pancreatitis. Approximately 10%-12% have overt features at the the time of the first attack but the majority have features that may become apparent only over time, often associated with cigarette smoking, recurrent and/or necrotizing attacks of pancreatitis.[40,41]

creatic cancer screening is a conditional recommendation of the ACG guidelines in patients with unexplained AP, particularly those aged 40 years or older.[1]

Etiology and diagnosis

Alcohol and gallstones remain the most prevalent etiologies for AP.[1] While hypertriglyceridemia accounted for 9% of AP in a systematic review of acute pancreatitis in 15 different countries,[38] it is the second most common cause of acute pancreatitis in Asia (especially China).[39] Figure 1 provides a breakdown of the etiologies and risk factors of pancreatitis. Importantly, it remains challenging to assign several toxic-metabolic etiologies as either a cause or risk factor for AP, particularly with regards to alcohol, smoking, and cannabis to name a few.

Guidelines and recent studies of AP raise questions about the threshold above which hypertriglyceridemia causes or poses as an important cofactor for AP. American and European societies define the threshold for triglycerides at 885-1,000 mg/dL.[1,42,43] Pedersen et al. provide evidence of a graded risk of AP with hypertriglyceridemia: In multivariable analysis, adjusted hazard ratios for AP were much higher with nonfasting mild to moderately elevated plasma triglycerides (177-885 mg/dL), compared with normal values (below 89 mg/dL).[44] Moreover, the risk of severe AP (developing POF) increases in proportion to triglyceride value, independent of the underlying cause of AP.[45]

Diagnosis of AP is derived from the revised Atlanta classification.[46] The recommended timing and indications for offering cross-sectional imaging are after 48-72 hours in patients with no improvement to initial care.[1] Endoscopic ultrasonography (EUS) has better diagnostic accuracy and sensitivity, compared with magnetic resonance cholangiopancreatography (MRCP) for choledocholithiasis, and has comparable specificity.[47,48] Among noninvasive imaging modalities, MRCP is more sensitive than computed tomography (CT) for diagnosing choledocholithiasis.[49] Despite guideline recommendations for more selective use of pancreatic imaging in the early assessment of AP, utilization of early CT or MRCP imaging (within the first 24 hours of care) remained high during 2014-2015, compared with 2006-2007.[50]

ERCP is not recommended as a pure diagnostic tool, owing to the availability of other diagnostic tests and a complication rate of 5%-10% with risks involving PEP, cholangitis, perforation, and hemorrhage.[51] A recent systematic review of EUS and ERCP in acute biliary pancreatitis concluded that EUS had lower failure rates and had no complications, and the use of EUS avoided ERCP in 71.2% of cases.[52]

Risk stratification

The goals of using risk stratification tools in AP are to identify patients at risk for developing major outcomes, including POF, infected pancreatic necrosis, and death, and to ensure timely triaging of patients to an appropriate level of care. Existing prediction models have only moderate predictive value.[53,54] Examples include simple risk stratification tools such as blood urea nitrogen (BUN) and hemoconcentration,[55,56] disease-modifying patient variables (age, obesity, etc.), biomarkers (i.e., angiopoietin 2),[57] and more complex clinical scoring systems such as Acute Physiology and Chronic Health Evaluation II (APACHE II), BISAP (BUN, impaired mental status, SIRS criteria, age, pleural effusion) score, early warning system (EWS), Glasgow-Imrie score, Japanese severity score, and recently the Pancreatitis Activity Scoring System (PASS).[58] Two recent guidelines affirmed the importance of predicting the severity of AP, using one or more predictive tools.[1,2] The recent 2018 AGA technical review does not debate this commonsense approach, but does highlight that there is no published observational study or randomized, controlled trial (RCT) investigating whether prediction tools affect clinical outcomes.[4]

Recent advances in early treatment of AP

Literature review and definitions

The AP literature contains heterogeneous definitions of severe AP and of what constitutes a major outcome in AP. Based on definitions of the 2013 revised Atlanta Criteria, the 2018 AGA technical review and clinical guidelines emphasized precise definitions of primary outcomes of clinical importance in AP, including death, persistent single organ failure, or persistent multiple organ failure, each requiring a duration of more than 48 hours, and infected pancreatic or peripancreatic necrosis or both (Table 2).[3,4]

TABLE 2
2013 revision of Atlanta criteria for AP severity

Severity of AP	Definitions
Mild	Absence of organ failure and Absence of local complications
Moderately severe	Local complications* and/or Transient organ failure (<48 hours)
Severe	Persistent organ failure (>48 hours)

* Local complications defined by one or more of the following: peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected), gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis.

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Pain management

Management of pain in AP is complex and requires a detailed discussion beyond the scope of this review, but recent clinical and translational studies raise questions about the current practice of using opioids for pain management in AP. A provocative, multicenter, retrospective cohort study reported lower 30-day mortality among critically ill patients who received epidural analgesia versus standard care without epidural analgesia.[59] The possible mechanism of protection and the drugs administered are unclear. An interesting hypothesis is that the epidural cohort may have received lower exposure to morphine, which may increase gut permeability, the risk of infectious complications, and severity of AP, based on a translational study in mice.[60]

Intravenous fluid administration

Supportive care with the use of IV fluid hydration is a mainstay of treatment for AP in the first 12-24 hours. Table 3 summarizes the guidelines in regards to IV fluid administration as delineated by the ACG and AGA guidelines on the management of pancreatitis.[1,3] Guidelines advocate for early fluid resuscitation to correct intravascular depletion in order to reduce morbidity and mortality associated with AP.[1,2,4] The 2018 AGA guidelines endorse a conditional recommendation for using goal-directed therapy for initial fluid management,[3] do not recommend for or against normal saline versus lactated Ringer's (LR), but do advise against the use of hydroxyethyl starch fluids.[3] Consistent with these recommendations, two recent RCTs published subsequent to the prespecified time periods of the AGA technical review and guideline, observed no significant differences between LR and normal saline on clinically meaningful outcomes.[61,62] The AGA guidelines acknowledge that evidence was of very-low quality in support of goal-directed therapy,[3,4] which has not been shown to have a significant reduction in persistent multiple organ failure, mortality, or pancreatic necrosis, compared with usual care. As the authors noted, interpretation of the data was limited by the absence of other critical outcomes in these trials (infected pancreatic necrosis), lack of uniformity of specific outcomes and definitions of transient and POF, few trials, and risk of bias. There is a clear need for a large RCT to provide evidence to guide decision making with fluid resuscitation in AP,

Continued on following page

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particularly in regard to fluid type, volume, rate, duration, endpoints, and clinical outcomes.

Feeding

More recently, the focus of nutrition in the management of AP has shifted away from patients remaining nil per os (NPO). Current guidelines advocate for early oral feeding (within 24 hours) in mild AP,[3,4] in order to protect the gut-mucosal barrier. Remaining NPO when compared with early oral feeding has a 2.5-fold higher risk for interventions for necrosis.[4] The recently published AGA technical review identified no significant impact on outcomes of early versus delayed oral feeding, which is consistent with observations of a landmark Dutch PYTHON trial entitled "Early versus on-demand nasoenteric tube feeding in acute pancreatitis."[4,63] There is no clear cutoff point for initiating feeding for those with severe AP. A suggested practical approach is to initiate feeding within 24-72 hours and offer enteral nutrition for those intolerant to oral feeds. In severe AP and moderately severe AP, enteral nutrition is recommended over parenteral nutrition.[3,4] Enteral nutrition significantly reduces the risk of infected peripancreatic necrosis, single organ failure, and multiorgan failure.[4] Finally, the AGA guidelines provide a conditional recommendation for providing enteral nutrition support through either the nasogastric or nasoenteric route.[3] Further studies are required to determine the optimal timing, rate, and formulation of enteral nutrition in severe AP.

Antibiotics and probiotics

Current guidelines do not support the use of prophylactic antibiotics to prevent infection in necrotizing AP and severe AP.[1-3] The AGA technical review reported that prophylactic antibiotics did not reduce infected pancreatic or peripancreatic necrosis, persistent single organ failure, or mortality.[4] Guidelines advocate against the use of probiotics for severe AP, because of increased mortality risk.[1]

Timing of ERCP in acute biliary pancreatitis

There is universal agreement for offering urgent ERCP (within 24 hours) in biliary AP complicated by cholangitis.[1-3,64] Figure 2 demonstrates an example of a cholangiogram completed within 24 hours of presentation of biliary AP complicated by cholangitis.

In the absence of cholangitis, the timing of ERCP for AP with persistent biliary obstruction is less clear.[1-3] In line with recent guidelines, the 2018 AGA guidelines advocate against routine use of urgent ERCP for biliary AP without cholangitis,[3] a conditional recommendation with overall low quality of data.[4] The AGA technical review found that urgent ERCP, compared with conservative management in acute biliary pancreatitis without cholangitis had no significant effect on mortality, organ failure, infected pancreatic necrosis, and total necrotizing pancreatitis, but did significantly shorten hospital length of stay.[4] There are limited data to guide decision making of when nonurgent ERCP should be performed in hospitalized patients with biliary AP with persistent obstruction and no cholangitis.[3,64]

Alcohol and smoking cessation

The AGA technical review advocates for brief alcohol intervention during hospitalization for alcohol-induced AP on the basis of one RCT that addresses the impact of alcohol counseling on recurrent bouts of AP[4] plus evidence from a Cochrane review of alcohol-reduction strategies in primary care populations.[65] Cessation of smoking – an established independent risk factor of AP – recurrent AP and chronic pancreatitis, should also be recommended as part of the management of AP.

TABLE 3

Comparison of guidelines on fluid administration for AP

Guideline	Recommendations for fluid resuscitation	Level of evidence
2013 ACG guideline	250-500 cc/hr crystalloid day 1 • Lactated Ringer's (LR) preferred over normal saline • Goal: Hydrate to decrease BUN	Strong recommendation Moderate quality data
2018 AGA guideline	Early goal-directed fluid therapy • No recommendation for/against using normal saline vs. LR • Recommend against use of hydroxyl ethyl starch	Conditional recommendation Very low quality data

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Note: Each guideline also cautions to balance under- vs. over-resuscitation to avoid worsening CHF, triggering abdominal compartment syndrome and increasing complications and mortality.

Cholecystectomy

Evidence supports same-admission cholecystectomy for mild gallstone AP, a strong recommendation of published AGA guidelines.[3] When compared with delayed cholecystectomy, same-admission cholecystectomy significantly reduced gallstone-related complications, readmissions for recurrent pancreatitis, and pancreaticobiliary complications, without having a significant impact on mortality during a 6-month follow-up period.[66] Delaying cholecystectomy 6 weeks in patients with moderate-severe gallstone AP appears to reduce morbidity, including the development of infected collections, and mortality.[4] An ongoing RCT, the APEC trial, aims to determine whether early ERCP with biliary sphincterotomy reduces major complications or death when compared with no intervention for biliary AP in patients at high risk of complications.[67]

Chemoprevention and IV fluid management of post-ERCP pancreatitis

Accumulating data support the effectiveness of chemoprevention, pancreatic stent placement, and fluid administration to prevent post-ERCP pancreatitis. Multiple RCTs, meta-analyses, and systematic reviews indicate that rectal NSAIDs) reduce post-ERCP pancreatitis onset[68-71] and moderate-severe post-ERCP pancreatitis. Additionally, placement of a pancreatic duct stent may decrease the risk of severe post-ERCP pancreatitis in high-risk patients.[3] Guidelines do not comment on fluid administrations for prevention of post-ERCP pancreatitis, but studies have shown that greater periprocedural IV fluid was an independent protective factor against moderate to severe PEP[72] and was associated with shorter hospital length of stay.[73] Recent meta-analyses and RCTs support using LR prior to ERCP to prevent PEP.[74-77] Interestingly, a recent RCT shows that the combination of rectal indomethacin and LR, compared with combination placebo and normal saline reduced the risk of PEP in high-risk patients.[78]

Two ongoing multicenter RCTs will clarify the role of combination therapy. The Dutch FLUYT RCT aims to determine the optimal combination of rectal NSAIDs and periprocedural infusion of IV fluids to reduce the incidence of PEP and moderate-severe PEP[79] and the Stent vs. Indomethacin (SVI) trial aims to determine the whether combination pancreatic stent placement plus rectal indomethacin is superior to monotherapy indomethacin for preventing post-ERCP pancreatitis in high-risk cases.[80]

Implications for clinical practice

The diagnosis and optimal management of AP require a systematic approach with multidisciplinary decision making. Morbidity and mortality in AP are driven by early or late POF, and the latter often is triggered by infected necrosis. Risk stratification of these patients at the point of contact is a common-sense approach to enable triaging of patients to the appropriate level of care. Regardless of pancreatitis severity, recommended treatment interventions include goal-directed IV fluid resuscitation, early feeding by mouth or enteral tube when necessary, avoidance of prophylactic antibiotics, avoidance of probiotics, and urgent ERCP for patients with acute biliary pancreatitis complicated by cholangitis. Key measures for preventing hospital readmission and pancreatitis include same-admission cholecystectomy for acute biliary pancreatitis and alcohol and smoking cessation. Preventive measures for post-ERCP pancreatitis in patients undergoing ERCP include rectal indomethacin, prophylactic pancreatic duct stent placement, and periprocedural fluid resuscitation.

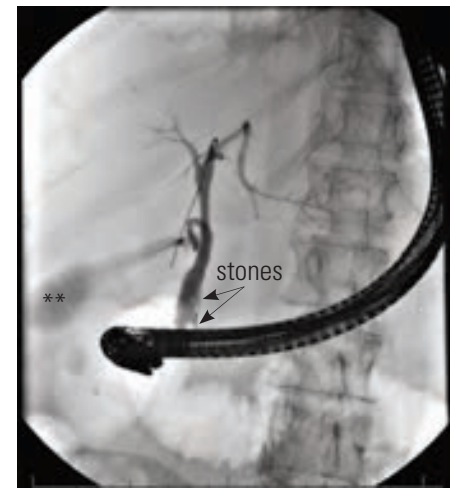

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Figure 2. Urgent ERCP for acute biliary pancreatitis with cholangitis: ERCP was performed within the first 24 hours. Cholangiogram showed biliary dilation to 9 mm, choledocholithiasis (stones), and gallbladder filling (**), the latter excluding cholecystitis. Therapy included biliary sphincterotomy and balloon pull through yielding stones, sludge, and pus.

See references at www.mdedge.com/gihepnews/new-gastroenterologist

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AGA GUIDELINE

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Guideline *from page 1*

but this outcome is more likely when patients are diagnosed before age 40 years or have extensive disease or deep ulcers, extraintestinal manifestations, or elevated inflammatory markers. These higher-risk patients need more aggressive initial treatment and faster treatment intensification in cases of inadequate response, the guideline emphasizes. Even for cases of mild to moderate ulcerative colitis, treatment intensification is preferable to repeated courses of corticosteroids.

The guideline recommends adding rectal mesalamine to oral 5-ASA if patients have extensive or left-sided mild to moderate ulcerative colitis. In randomized controlled trials, this combination was significantly more likely to induce and maintain remission than was standard-dose oral mesalamine monotherapy, the authors noted. "In the maintenance trials, enemas were used twice per week or for 1 week per month. Both oral and topical mesalamine were well tolerated."

For patients with moderate disease activity or a suboptimal response to standard-dose mesalamine or diazo-bonded 5-ASA, the guideline recommends adding rectal mesalamine to high-dose oral mesalamine (more than 3 grams daily). Combination therapy maximizes the delivery of mesalamine to the affected area of the colon, which optimizes the trial of 5-ASA before opting for treatment escalation, the authors noted. They recommend once-daily oral mesalamine dosing, since this is easier to adhere to and studies have found no benefit of more frequent dosing.

For inducing remission of mild to moderate ulcerative colitis, the guideline recommends standard-dose oral mesalamine or diazo-bonded 5-ASA over budesonide. "Overall, the budesonide preparations are not superior to mesalamine for induction of remission," the authors wrote. Oral 5-ASAs are preferred, especially given the absence of data on the efficacy or safety of maintenance budesonide therapy.

For patients with mild to moderate ulcerative proctosigmoiditis or proctitis, the guideline conditionally recommends rectal mesalamine over oral mesalamine. Compared with placebo, rectal mesalamine suppositories were significantly more likely to induce remission in randomized trials of patients with mild to moderate ulcerative proctitis. If these patients cannot tolerate or are refractory to mesalamine suppositories, low-quality evidence supports rectal steroid therapy over no treatment, the guideline states. For patients with mild to moderate ulcerative proctosigmoiditis, moderate-quality evidence supports mesalamine enemas over rectal corticosteroids. If these patients want to avoid the difficulties of enemas, the guideline considers rectal corticosteroid foam a reasonable alternative.

Likewise, they cite low-quality evidence for adding oral prednisone or budesonide MMX to 5-ASA if patients are refractory to optimized 5-ASA therapy. No trials have directly compared rates of remission with budesonide MMX versus systemic corticosteroids. In just one placebo-controlled trial, adding budesonide MMX to 5-ASA slightly improved the chances of remission (risk ratio, 0.95; 95% confidence interval, 0.89-1.00). Furthermore, studies of other second-generation corticosteroids found they were better tolerated but no more likely to induce remission than oral prednisone or prednisolone.

Some patients with mild to moderate colitis respond inadequately to these recommended therapies and need systemic corticosteroids, immunomodulators, or biologic therapies to induce and maintain remission, the guideline authors noted. They make no recommendation on immunomodulators or biologics. Studies of probiotics, curcumin, and fecal microbiota transplantation are "urgently needed," but for now, their use "risks delaying proven effective therapy, with the potential for worsening symptoms or complications," they wrote. For patients without *Clostridium difficile* infections, they recommend against fecal microbiota transplantation except in the setting of a clinical trial.

The experts also noted the need for a tool to stratify patients with mild to moderate ulcerative colitis based on their risk of future progression and colectomy.

Finally, they call for studies on who will benefit most from high-dose mesalamine or topical mesalamine and on the relative safety and efficacy of budesonide and systemic corticosteroids in the event of an inadequate response to 5-ASAs.

No conflicts of interest or outside funding sources were reported.

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SOURCE: Crocket SD et al. Gastro. 2019;156(2) doi: org/10.1053/j.gastro.2018.12.009..

Differences in gut bacteria can distinguish IBD from IBS

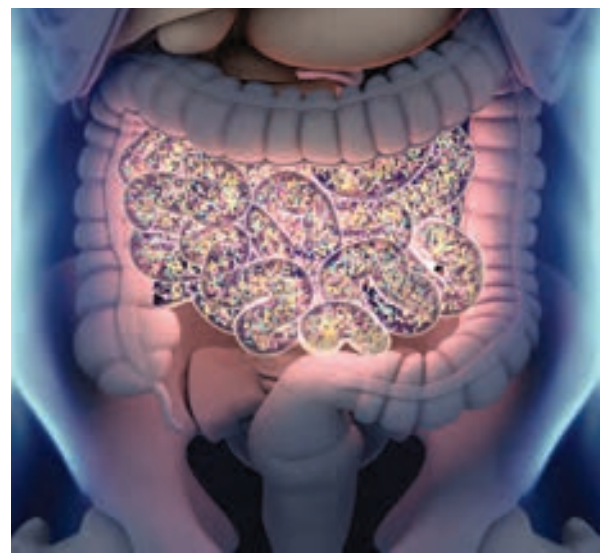
BY STEVE CIMINO
MDedge News

Thanks to shotgun metagenomic sequencing of gut microbiota, physicians are on track to more easily distinguish inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS), according to an analysis of stool samples from patients with the two common gastrointestinal diseases.

"The integration of these datasets allowed us to pinpoint key species as targets for functional studies in IBD and IBS and to connect knowledge of the etiology and pathogenesis of IBD and IBS with the gut microbiome to provide potential new targets for treatment," wrote Arnau Vich Vila, of the University of Groningen (the Netherlands) and his coauthors. The report is in Science Translational Medicine.

Stool samples from 1,792 participants were analyzed: 355 from patients with IBD, 412 from patients with IBS, and 1,025 from the control group. The researchers found 24 bacterial taxa associated with both IBD and IBS and specific species that accompanied specific diseases, such as an abundance of Bacteroides in patients with IBD and Firmicutes in patients with IBS. In addition, their predictive model to distinguish IBD from IBS via gut microbial composition data [area under the curve $(AUC)_{mean}$ = 0.91 (0.81-0.99)] proved more accurate than did current fecal biomarker calprotectin [AUC_{mean} = 0.80 (0.71-0.88); P = .002].

The authors acknowledged additional evidence that will be needed before these results can be translated to clinical practice, including supporting their described microbial pathways with metatranscriptomics and metabolomics data as well as functional experiments. They also observed that their predictive model will need to be validated through replication of their findings in patients with other gastrointestinal disorders or prediagnostic groups.



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They noted that their analysis benefited from being able to correct for confounding factors such as medication use, which is "essential for identifying disease-associated microbial features and avoiding false-positive associations due to changes in GI acidity or bowel mobility."

One author reported receiving speaker fees from AbbVie and was a shareholder of the health care IT company Aceso BV and of Floris Medical Holding BV. Another author declared unrestricted research grants from AbbVie, Takeda, and Ferring Pharmaceuticals, is on the advisory boards for Mundipharma and Pharmacosmos, and has received speaker fees from Takeda and Janssen Pharmaceuticals. A third author declared consulting work for Takeda. The others reported no conflicts of interest.

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SOURCE: Vich Vila A et al. Sci Transl Med. 2018 Dec 19. doi: 10.1126/scitranslmed.aap8914.

AGA CLINICAL PRACTICE UPDATE

Functional gastrointestinal symptoms in patients with inflammatory bowel disease

BY AMY KARON
MDedge News

When patients with inflammatory bowel disease report persistent gastrointestinal symptoms, clinicians should perform a thorough clinical assessment and then take a stepwise approach to rule out ongoing inflammation, according to a clinical practice update from the American Gastroenterological Association.

A fecal calprotectin test can be useful because values under 50 mcg/mL may suggest endoscopic remission, which may, in turn, point to another etiology of gastrointestinal symptoms, wrote Jean-Frederic Colombel, MD, of the Icahn School of Medicine at Mount Sinai, New York, together with his associates in Clinical Gastroenterology and Hepatology.

However, a result between 50 and 250 mcg/mL is harder to interpret because the upper limit of normal varies and mild increases can occur secondary to nonspecific low-grade inflammation, according to the experts. For mild gastrointestinal symptoms, they suggested testing fecal calprotectin every 3-6 months to identify flares as early as possible. If a flare is suspected, they advised considering cross-sectional imaging or endoscopy with biopsy.

Imaging also is indicated for patients with obstructive symptoms such as abdominal pain, obstipation, or constipation, the practice update states. Such symptoms can indicate fecal stasis proximal to distal colitis in patients with ulcerative colitis, or intestinal stenosis in patients with Crohn's disease.

Other pathophysiologies of gastrointestinal symptoms also should be considered based on constellations of symptoms. For example, steatorrhea with chronic abdominal pain may indicate pancreatic exocrine insufficiency, which fecal elastase testing can help confirm. Symptoms of diarrhea-predominant irritable bowel syndrome can result from bile acid diarrhea, for which several screening tests are available. Diarrhea, abdominal pain, and bloating may indicate carbohydrate malabsorption or small-intestinal bacterial overgrowth, which can be evaluated with breath testing.


Dr. Jean-Frederic Colombel

If patients with inflammatory bowel disease have persistent gastrointestinal symptoms but lack objective evidence of ongoing inflammation or another etiology, then clinicians should increase their suspicion of an overlapping functional gastrointestinal disorder. These conditions actually "share many common pathophysiologic disturbances that, in some inflammatory bowel disease patients, may be a consequence of prior structural and functional bowel damage," the experts wrote.

For patients with chronic constipation who do not have an underlying obstruction, they suggest osmotic or stimulant laxatives. For chronic diarrhea, they recommend hypomobility agents or bile-acid sequestrants. Patients with fecal symptoms of irritable bowel syndrome also should be evaluated for pelvic floor disorders, which may improve with biofeedback therapy, the experts state.

A low-FODMAP diet (a diet low in lactose, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) also can improve symptoms of irritable bowel syndrome, including patients with inflammatory bowel disease. However, a dietitian always should deliver this restrictive diet because patients with inflammatory bowel disease already are at increased risk for undernutrition.

Patients with functional gastrointestinal pain may benefit from antispasmodics, neuropathic-directed agents, and antidepressants, but they should not receive opiates, the experts emphasized. Anxiety and depression are common in both inflammatory bowel disease and irritable bowel syndrome, and patients may benefit from psychotherapy (cognitive-behavioral therapy, hypnotherapy, and mindfulness therapy), antidepressants, anxiolytics, or combinations of these treatments. The practice update also recommends physical exercise, which has been shown to decrease the risk of recurrent active disease in the setting of inflammatory bowel disease.

Finally, persistent gut symptoms can indicate intestinal barrier dysfunction, even if endoscopy shows mucosal healing. Barrier dysfunction is a potential therapeutic target that needs further study in this setting, the experts noted. They also called for studies of the potential benefits and risks of probiotics and other alternative approaches, such as herbal treatments and supplements, yoga, acupuncture, and moxibustion. Until further evidence, however, they have recommended against complementary or alternative medicine or fecal microbiota transplantation.

Dr. Colombel has served as consultant, advisory board member, or speaker for AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, and many other pharmaceutical companiesa. He has received research grants from AbbVie, Takeda, Janssen and Janssen.

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SOURCE: Colombel J-F et al. Clin Gastroenterol Hepatol. 2018 Aug 9. doi: 10.1016/j.cgh.2018.08.001.

NIH announces new clinical trial assessing FMT

BY LUCAS FRANKI
MDedge News

A clinical trial has begun which will examine whether fecal microbiota transplantation (FMT) by enema is safe and can prevent recurrent *Clostridium difficile*–associated disease (CDAD), according to a press release from the National Institutes of Health.

CDAD is normally treated with antibiotics such as vancomycin or fidaxomicin; however, it recurs in about 20% of people who receive this treatment. FMT, administered by oral pill, upper endoscopy, and enema, is effective at curing patients with recurring *C. diff* infections, but long-term safety and a standardized process have yet to be established.

An estimated 162 people aged 18 years or older who have had two or more episodes of CDAD within the previous 6 months will be included in the clinical trial. These patients will be split into two groups: The first will receive an antidiarrheal medication and an FMT delivered by retention enema; the second will receive an antidiarrheal and a placebo colored to look like an active stool sample. If patients in either group have diarrhea with stools that test positive for *C. diff* shortly after the enema, thet will receive an active stool transplant.

Trial sites will include Emory University in Atlanta, Duke University Medical Center in Durham, N.C., and Vanderbilt University Medical Center in Nashville, Tenn. All patients will provide stool and blood samples at designated time points for 1 year after they undergo treatment for CDAD. Stool samples will be examined for gut microbial diversity changes and infectious pathogens; blood samples will be examined for metabolic syndrome markers. Participants will be monitored for adverse side effects for 3 years after the trial.

Stool samples will be examined for gut microbial diversity changes and infectious pathogens; blood samples will be examined for metabolic syndrome markers.

"*Clostridium difficile*–associated disease, a significant problem in health care facilities, causes an estimated 15,000 deaths in the United States each year. This randomized, controlled trial aims to provide critical data on the efficacy and long-term safety of using fecal microbiota transplants by enema to cure *C. diff* infections," National Institute for Allergy and Infectious Diseases director Anthony S. Fauci, MD, said in the press release.

The full trial page can be found at Clinicaltrials.gov.

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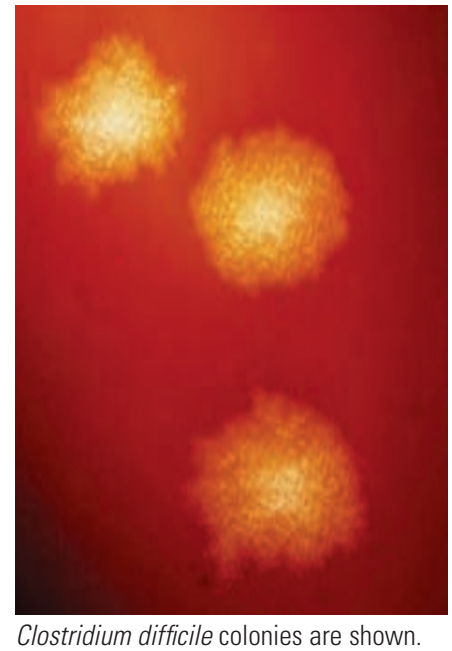

CDC/Dr. Holdeman

Clostridium difficile colonies are shown.

Postdiagnosis statin use lowers mortality rate for patients with HCC

BY JEFF CRAVEN
MDedge News

Statin use after a diagnosis of hepatocellular carcinoma (HCC) was associated with a reduced risk of all-cause and cancer-specific mortality, according to recent research published in Clinical Gastroenterology and Hepatology.

"Our current findings are biologically plausible since statins inhibit not only cholesterol synthesis but also reduce other important downstream products, including membrane integrity maintenance, cell signaling, protein synthesis, and cell-cycle progression," wrote Aaron P. Thrift, PhD, of the section of epidemiology and population sciences and department of medicine at Baylor College of Medicine in Houston, and his colleagues.

"Not only can statins have a direct impact on cancer cells through inhibition of the mevalonate pathway within the cancer cells, but the reduction of circulating cholesterol levels through hepatic pathways is indeed considered important," he said.

Dr. Thrift and his colleagues performed a retrospective cohort analysis of data from 15,422 patients with HCC in the VA Central Cancer Registry who were diagnosed between 2002 and 2016 and filled a prescription for statins. The researchers looked at statin prescriptions filled prior to and after diagnosis, following patients from diagnosis up to a 3-month lag period. The statins analyzed included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin.

Patients who used statins after diagnosis had a median survival time of 26.38 months compared with 15.67 months for patients who did not use statins after diagnosis.

Overall, 78.8% of patients died during 26,680 person-years of follow-up and the median survival time was 17.24 months. The researchers found 14.9% of patients (2,293 patients) with HCC filled prescriptions for statins after their cancer diagnosis. The median time to begin statins after diagnosis was 2.37 months, and patients who used statins after diagnosis had a median survival time of 26.38 months compared with 15.67 months for patients who did not use statins after diagnosis.

For HCC patients who used statins, there was a decreased risk of all-cause mortality (hazard ratio, 0.89; 95% confidence interval, 0.83-0.95) and cancer-specific mortality (adjusted HR, 0.85; 95% CI, 0.77-0.93), which was consistent for both high-dose and low-dose statins and for lag periods between 0 months and 12 months after diagnosis.

Limitations in the study were the exclusion of any statins filled at non-VA pharmacies, baseline differences in statin users and non-statin users that could have affected results, potential misclassification of cirrhosis in the registry, and the lack of generalization to other populations due to a veteran-specific patient cohort.

This study was funded by the National Institutes of Health and VA Health Services Research and Development Service Center for Innovations in Quality, Effectiveness, and Safety. The authors report having no financial conflicts of interest.

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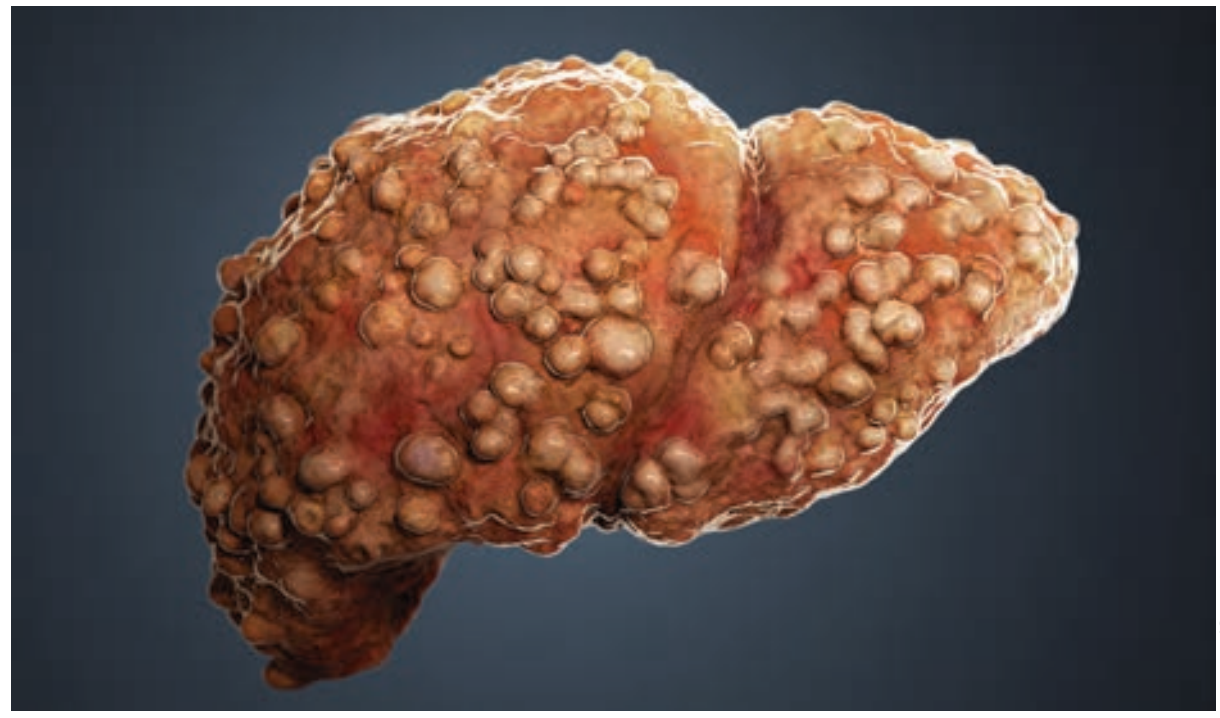
SOURCE: Thrift AP et al. Clin Gastroenterol Hepatol. 2019. doi: 10.1016/j.cgh.2018.12.046.

Low-normal thyroid function tied to advanced fibrosis

BY AMY KARON
MDedge News



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Advanced fibrosis affected 5.9% of adults with low-normal thyroid function or subclinical hypothyroidism – more than double the prevalence among adults with strict-normal thyroid function (2.8%; *P* less than .001), according to the results of a large survey study.

Based on these findings, therapy to improve low thyroid function might help prevent advanced fibrosis secondary to nonalcoholic fatty liver disease, wrote Donghee Kim, MD, PhD, of Stanford (Calif.) University, together with his associates in Clinical Gastroenterology and Hepatology.

Prior research has linked low-normal thyroid function with obesity, cardiometabolic diseases, and fractures. For this study, Dr. Kim and his coinvestigators analyzed data from 7,259 adults who lacked major etiologies of chronic liver disease and were included in the National Health and Nutrition Examination Survey between 2007 and 2012.

After demographic, socioeconomic, and clinical variables were considered, the odds of biopsy-confirmed advanced fibrosis were 100% higher in adults with low-normal thyroid function or subclinical hypothyroidism, compared with adults with strict-normal thyroid function (odds ratio, 2.0; 95% confidence interval, 1.2-3.3). The prevalence and odds of advanced fibrosis was similar in each of these two subgroups. Furthermore, low thyroid function remained strongly linked with advanced fibrosis after accounting for insulin resistance using data from fasting subjects (OR, 2.3; 95% CI, 1.2-4.4).

Previously, Dr. Kim and his coinvestigators found a strong link between biopsy-proven advanced fibrosis and low-normal thyroid function or subclinical hypothyroidism among adults in Korea. "These [new] results are consistent with our previous observations in [an] Asian population, and show their generalizability to the Western world across all ethnicities."

The researchers did not acknowledge external funding sources. They reported having no conflicts of interest.

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SOURCE: Kim D et al. Clin Gastroenterol Hepatol. 2018 Nov 17. doi: 10.1016/j.cgh.2018.11.024.

Real-world weight loss with meds approximates RCT data

BY KARI OAKES
MDedge News

NASHVILLE, TENN. – Patients who took a fixed-dose combination of phentermine and topiramate–extended release (ER) lost over 15% of their body weight at 12 months, according to real-world experience at the Mayo Clinic in Rochester, Minn.

The results seen with the medication combo – a mean 15.5% total body weight loss at 12 months – bested the 8%-11% seen in randomized controlled trials (RCTs), said Gerardo Calderon, MD, in an interview during a poster session at Obesity Week, presented by the Obesity Society and the American Society for Metabolic and Bariatric Surgery. The combination was also the most commonly prescribed weight loss medication at the Mayo Clinic, where Dr. Calderon is a gastroenterology and hepatology research fellow.

Dr. Calderon

Patients taking lorcaserin at the Mayo Clinic also lost more weight than RCT participants (8.8% vs. 5%-6%, respectively). They also had a higher probability of losing at least 10% of their baseline body weight (40% vs. 17%-23% in clinical trials). In RCTs, 37%-48% of patients taking phentermine/topiramate-ER had a body weight loss of at least 10%, similar to the Mayo Clinic's figure of 49%.

The rate of reported adverse events – 23.8% – exceeded that reported in RCTs, noted Dr. Calderon. Gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and constipation, were reported by 2%-20% of patients across the various drugs prescribed. Insomnia and mood changes, along with dizziness or lightheadedness, were reported by 2%-6% of patients. Almost 12% of patients taking phentermine/topiramate-standard release (SR) reported paresthesias. No patients stopped taking their medication because of side effects, however.

The study was a review of patients seen at the Mayo Clinic during January 2016 – June 2018. Patients were included if they were prescribed weight loss medications and had a body mass index of at least 25 kg/m^2 with comorbidities related to adiposity or with a BMI of at least 30 without such comorbidities. To be included, patients had to be followed for at least 3 months and see a Mayo Clinic physician at least twice.

Patients with previous bariatric surgery or other major gastrointestinal surgery, those who didn't use their medications because of insurance problems or drug costs, and those who were on weight loss medication before being seen for the first time were excluded from the study.

Patients were a mean 49 years old, and most were female (86/118; 72.9%). Mean BMI at enrollment was 41.7, with a mean weight of 117.6 kg.

Of 118 patients, 76 (64.4%) had dyslipidemia. About half reported obstructive sleep apnea, and the same amount had hypertension. About 40% had diabetes, and the same number had degenerative joint disease.

Phentermine/topiramate was prescribed the most frequently; 43.2% of patients took this medication. Liraglutide was taken by 34.7% of patients, bupropion/naltrexone-SR by 16.1%, and lorcaserin by 5.9%.

For bupropion/naltrexone-SR, weight loss was similar among the Mayo Clinic patients (7.2%) and RCT participants (5%-8%), and probability of achieving at least 10% total body weight loss was similar (32% vs. 34%).

Weight loss medication was a component of a multidisciplinary weight loss approach at Mayo Clinic. Physicians, dietitians, and psychologists worked together to care for patients with overweight and obesity at his facility, Dr. Calderon said. Overall, patients were followed for a mean 6.7 months, and patients had a mean three follow-up visits, with over half of patients attending at least one follow-up appointment in study months 6-12. At 12 months, though, the attrition rate was 57.9%. "Definitely, this is something we are concerned about, and we would like to bring these attrition rates lower," he said.

Dr. Calderon reported no outside sources of funding and no conflicts of interest.

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SOURCE: Calderon G et al. Obesity Week, Abstract T-P-3425.

Suit claims monopoly on MOC

ABIM *from page 1*

questions addressing specific accusations from the lawsuit. However, in an interview, ABIM President Richard Baron, MD, said that "ABIM board-certified physicians have taken the initiative to distinguish themselves. This is a credential that physicians earn. We offer certified physicians the opportunity to demonstrate to the medical community, their peers, and the public that they are current and have special expertise."

At this article's deadline, ABIM had not yet filed a formal response to the lawsuit. Court documents show that, in January, ABIM entered the appearances of four attorneys that will represent the board in the case. From there, discovery and evidence gathering in the case will begin.

Katherine Murray Leisure, MD, an infectious disease specialist based in Plymouth, Mass., is one of the plaintiffs. While she said that she could not comment specifically on the lawsuit, she has written publicly about her ABIM concerns in the past.

In a 2015 letter to Dr. Baron and posted on an anti-MOC website, Dr. Murray Leisure outlined a litany of complaints against ABIM's MOC process and called on the U.S. Congress to investigate ABIM's financial, legal, and ethical conduct.

"[The American Board of Medical Specialties] and ABIM collected more than $10,000 in fees and lost practice hours every decade from each [diplomate] doing MOC," Dr. Murray Leisure wrote. "MOC took weeks away from our offices, clinics, patients, families, specialty societies, and individual research. ABMS MOC removed hundreds, perhaps thousands … of America's best, once board-certified physicians from full hospital careers and earnings whenever [diplomates] did not complete these high-stakes MOC programs. … The righteous and fast solution to such moral, ethical, scientific, and constitutional problems is to end MOC now."

Plaintiffs Glen Dela Cruz Manalo, MD; Alexa Joshua, MD; and Gerard Kenney, MD, did not return messages seeking comment. When contacted, attorneys for the plaintiffs declined to comment.

The doctors' 32-page lawsuit characterizes ABIM as an organization motivated by money that has made its MOC process increasingly more burdensome for physicians over the years without evidence that MOC has any beneficial impact on doctors, patients, or the public. Complying with ABIM's MOC costs internists an average of $23,607 in financial cost and time lost over 10 years, and costs up to $40,495 for some specialists, according to the suit.

The physicians allege that ABIM controls in excess of 95% of the market for MOC of internists, in violation of federal antitrust laws, and that the organization has unlawfully obtained and maintained monopoly power for MOC services.

DR. BARON

The board's illegal tying of its initial certification to its MOC results in burdensome conditions, including "raising the cost of the practice of medicine, constraining the supply of internists thereby harming competition, decreasing the supply of certified internists, and increasing the cost of medical services to patients and consumers," the suit claims.

The legal challenge details how MOC has personally and professionally impacted each of the four plaintiffs. Dr. Manalo, a gastroenterologist, lost his privileges at St. Vincent Healthcare in Billings, Mont., and was subsequently terminated after he declined to maintain his ABIM certification as a gastroenterologist. In a letter to ABIM, Dr. Manalo wrote that it was "unfair and outright discriminatory that practitioners certified on or after 1990 are the only ones required to certify," according to the lawsuit. Dr. Manalo later took a position as staff gastroenterologist at Jonathan M. Wainwright Memorial Veterans Affairs Medical Center in Walla Walla, Wash., at a substantially reduced salary. He became unemployed in 2017.

Dr. Murray Leisure obtained an initial and lifelong board certification in internal medicine from ABIM in 1984 and an infectious disease certification in 1990. ABlM terminated Dr. Murray Leisure's infectious diseases certification after she failed her MOC examination in 2009, which led to lost privileges at Jordan Hospital in Plymouth. The loss caused significant damage to Dr. Murray Leisure, including lost income, a tarnished reputation, and the lost opportunity to help patients, according to the lawsuit. Jordan Hospital restored her privileges after Dr. Murray Leisure passed her MOC examination in 2012.

Dr. Kenney lost a job opportunity with Mount Nittany Physicians Group in State College, Pa., after he declined to renew his ABIM certification in gastroenterology. He is currently a physician with the University of Pittsburgh Medical Center in Seneca, Pa.

That the ABIM website lists him as "not certified," is misleading, and makes it appear that his initial certifications were revoked because of failure to pass a MOC examination or misconduct, rather than because the certifications lapsed, according to the suit. The description makes Dr. Kenney appear less qualified to patients, hospitals, insurance companies, medical corporations, other employers, and others, he claims.

Dr. Joshua could not renew her consulting and admitting privileges at Detroit Medical Center after she failed an MOC examination in 2014 and became uncertified in internal medicine, according to the suit. In addition, Blue Cross Blue Shield informed Dr. Joshua it would no longer cover her because it required ABIM certification for coverage. She unsuccessfully appealed based on her certification with the National Board of Physicians and Surgeons. As a result of her certification termination, Dr. Joshua can practice only outpatient medicine at Detroit Medical Center.

In an interview, Dr. Baron emphasized the number of modifications made to its MOC process in recent years after responding to physician concerns. This includes an overhaul of the organization's governance structure to include more than 200 practicing physicians and opening new avenues for physicians to engage in the creation of assessment content that more closely reflects what they see in practice, he said. In addition, ABIM now surveys all specialists to contribute to the exam blueprint review and the creation of the new Item Writing Task Force.

"We take all suggestions from physicians seriously, and have used it to launch many new initiatives including the Knowledge Check-In, a new Physician Portal, partnerships to give physicians dual credit for CME and MOC, and exploration of alternative assessment models with medical societies," he said.

Dr. Baron acknowledge past criticism of the MOC process, but said he is proud of the work ABIM has done to address physician concerns about the choice, relevance, and convenience of its MOC program.

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Doc groups pushing back on Part B drug reimbursement proposal

BY GREGORY TWACHTMAN
MDedge News

A proposal by the Trump Administration to pay for Medicare drugs administered in the physician office is not going over well with doctors.

The Centers for Medicare & Medicaid Services in October 2018 issued an "advance notice of proposed rulemaking with comment" outlining a test that would pay for Part B drugs with price points more closely aligned with international rates through the use of private sector vendors that would negotiate drug prices, procure the products, distribute them to physicians and hospitals, and take on the responsibility of billing Medicare.

Although the so-called International Pricing Index (IPI) model is not fully fleshed out in the regulatory filing, one of the key details that has been announced is that the demonstration project would have mandatory participation. This did not sit well with medical societies offering feedback to CMS.

The American Gastroenterological Association stated in comments filed with the agency that "AGA opposes mandatory physician participation and we urge CMS to implement the model on a voluntary basis." AGA further noted that, while they support the Administration's goal of reducing drug costs, "we are concerned that the model, as described, will make acquisition of Part B drugs more complex and will shift costs to physicians and practices, increasing administrative burden. Moreover, we are concerned that the IPI model may restrict access to clinically appropriate therapies for people with digestive diseases."

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A patient receives infusion drugs, which are currently under Part B.

And while the Community Oncology Alliance also spoke against making participation in the IPI model demonstration project mandatory, it went further with its criticism of the proposal.

"COA does not support the IPI Model as proposed in the pre-proposed rule published by [CMS] because we have serious concerns about its impact on cancer patient care and even its legality," the group said in Dec. 31, 2018, comments filed with the agency, adding that "mandatory demonstration projects are clearly not in the charter of CMMI [Center for Medicare & Medicaid Innovation] as written into law by Congress. ... That would either be illegal or unconstitutional, with the latter case invalidating the section of the law that created and funded CMMI."

The AGA, like other groups, also took exception to CMS's "insinuation" in its regulatory preproposal that physicians select treatments based on reimbursement ahead of patient need. "CMS has repeatedly suggested that physicians prescribe therapies to patients not based on clinical evidence and judgement, but rather based on how much Medicare revenue it will generate for them. AGA objects to this premise. There is no objective evidence to support this idea."

While none of the groups offered support for the IPI demonstration project, all offered suggestions on what could be done to improve on the details outlined in the advanced noticed of proposed rulemaking. AGA made recommendations, including making IPI Model participation voluntary; allowing individual physicians and physician groups to become model vendors, even if they intend to serve only their own practice or their own geographic region; prohibiting model vendors from implementing utilization management; and making model vendors responsible for collecting beneficiary cost-sharing.

The American Medical Association in Dec. 20, 2018, comments to the agency took issue with the focus on single-source drugs and biologics indexed with international pricing, which could create access issues and have immediate adverse patient impacts.

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Spending on medical marketing increased by $12.2 billion

BY STEVE CIMINO
MDedge News

Total spending on medical marketing in the United States increased from $17.7 billion in 1997 to $29.9 billion in 2016, according to an analysis of direct-to-consumer (DTC) and professional marketing for prescription drugs, disease awareness campaigns, health services, and laboratory tests.

"Increased medical marketing reflects a convergence of scientific, economic, legal, and social forces," wrote Lisa M. Schwartz, MD, and her coauthor, adding that, "although marketing expanded over 20 years, regulatory oversight remains relatively limited." Dr. Schwartz, then codirector of the Center for Medicine and Media at The Dartmouth Institute in Lebanon, N.H., died in November of 2018, after her work was accepted for publication in JAMA.

Dr. Schwartz and her coauthor, David Woloshin, MD, also of Dartmouth, reviewed consumer advertising and professional marketing data, along with searches of medical literature and business journals, to ascertain the quantity and impact of spending. The most money was spent on marketing to medical professionals, which increased from $15.6 billion in 1997 to $20.3 billion in 2016. In terms of percentages, the biggest increase was seen in DTC advertising: $2.1 billion in 1997 (11.9% of total spending) ballooned to $9.6 billion (32.1% of total spending).

These increases were not accompanied by corresponding regulatory efforts to limit influence or protect patients and consumers. In 2016, the Food and Drug Administration's Office of Prescription Drug Promotion received 97,252 promotional materials that drug companies submitted for review, compared with 34,182 in 1997, but violation letters for prescription drug advertising decreased from 156 to 11. In the same year, the FDA reviewed 41% of core materials – such as risk disclosures and key messages – for new drugs or indications prior to launch, a performance measure the coauthors called "critically important."

In regard to disease awareness campaigns, 2004 guidance from the FDA on awareness advertising – including standards for unbranded campaigns and recommendations to avoid encouraging self-diagnosis and self-treatment – was withdrawn in 2015 and never replaced. The Federal Trade Commission, which has jurisdiction over unbranded advertising, has not taken regulatory action of its own; any FDA requests for investigation are unknown. In addition, these 2 decades have not seen state attorneys general initiate any action against deceptive consumer advertising, nor has the FTC acted against misleading laboratory test promotion.

"The FDA and FTC should establish and enforce standards for responsible disease awareness campaigns," the coauthors wrote, "including criteria to validate symptom quizzes (or banning them) and evidence-based strategies to minimize misconceptions that a drug can treat all symptoms of disease."

Overall, spending on medical marketing actually increased faster than did spending on health services overall. Marketing saw a remarkable 430% increase ($542 million to $2.9 billion) over the 2 decades, while health services spending increased by 90% ($1.2 trillion to $2.2 trillion).

One of the rare similarities from 1997 to 2016 was spending on marketing prescription drugs to physicians, typically through face-to-face meetings and hospital visits; this held steady at approximately $5 billion. However, spending on drug samples increased from $8.9 billion to $13.5 billion, while medical journal advertising declined drastically from

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PROFESSIONAL OPPORTUNITIES

Parental leave for residents less than for faculty

BY STEVE CIMINO
MDedge News

Leave policies for residents who become new parents are uneven, oft-ignored by training boards, and provide less time off than similar policies for faculty physicians. Those were the findings of a pair of research letters published in JAMA.

Kirti Magudia, MD, of the department of radiology at Brigham and Women's Hospital in Boston and her colleagues reviewed childbearing and family leave policies for 15 graduate medical education (GME)–sponsoring institutions, all of which were affiliated with the top 12 U.S. medical schools. Though all 12 schools provided paid childbearing or family leave for faculty physicians, only 8 of the 15 did so for residents (JAMA. 2018 Dec 11;320[22]:2372-4).

In programs that did provide leave, the average of 6.6 weeks of paid total maternity leave for residents was less than the 8.6 weeks faculty receive. Both are considerably less than proscribed by the Family and Medical Leave Act, which requires large employers to provide 12 weeks of unpaid leave, but only after 12 months of employment.

The research focused on only institutional policies for paid leave; unpaid leave and state policies may extend the average, and departments may offer leave that goes beyond specific policies, Dr. Magudia and her colleagues noted.

Changes in the residency population make now the right time for establishing consistent family leave policies, Dr. Magudia said in an interview. "We have people starting training later; we have more female trainees. And with the Match system, you're not in control of exactly where you're going. You may not have a support system where you end up, and a lot of the top training institutions are in high cost-of-living areas. All of those things together can make trainees especially vulnerable, and because trainees are temporary employees, changing policies to benefit them is very challenging.

"Making sure people have adequate parental leave goes a long way toward reducing stress levels and helping them cope with normal life transitions. We want to take steps that promote success among a di-

Continued on following page

PERSPECTIVE

Parental leave: Equal for all?

Recent data by Magudia et al. have highlighted the fact that family leave policies supporting parents during medical training are widely inconsistent and in many instances do not exist. Where trainee policies do exist, benefits are routinely less robust than those of permanent faculty who receive on average 30% more paid leave time. Stratifying physician wellness needs by training status seems to be a misplaced approach.

It is not only the medical field which sees inconsistencies in the way family leave is allocated for different types of jobs. Millions of Americans receive no time off after birth or adoption, at a time when corporate America offers elite benefits for child care. In medicine, however, there is an expectation that paid family leave should be the norm, perhaps because of our mission to improve the quality of health care.

Of course there are valid distinctions between faculty and trainees: faculty are more permanent, are more professionally differentiated and accomplished than trainees, have greater responsibilities, and are recruited for their expertise. Arguably, faculty deserve better compensation than trainees.

But the importance of parental leave transcends the routine benefits arguments. There is something more universal about how we value parenting. Parental leave policies benefit the health of parent and child, increase career satisfaction, and improve retention. The process of birth or adoption, ensuing fatigue, family bonding needs, and life-restructuring will challenge all parents regardless of career status.

Awareness of the inadequacies of parental leave policies is the first step in remedying the disparities in support for our trainees. Establishing an equal and adequate family leave policy for physicians at any stage is consistent with the goal of success and well-being for us all.

Laurel Fisher, MD, AGAF, professor of clinical internal medicine, division of gastroenterology, University of Pennsylvania, Philadelphia. She reports no conflicts of interest.

Continued from page 32

$744 million to $119 million.

Spending on DTC marketing of prescription drugs increased across all therapeutic categories but three: cholesterol, allergy, and osteoporosis, each of which saw top-selling drugs either become over-the-counter or lose patent protection. Spending on drugs for diabetes/endocrine disease went from $27 million in 1997 to a whopping $725 million in 2016, followed by dermatology drugs ($67 million to $605 million) and pain/central nervous system drugs ($56 million to $542 million).

The coauthors shared potential limitations of their study, including the likelihood that they underestimated how much is actually spent on medical marketing. "Data on professional marketing (e.g., detailing) of laboratory tests, health services or devices, and pharmaceutical company spending on coupons or rebates, online promotion, and meetings and events could not be obtained," they noted. In addition, company marketing budgets often do not include additional expenses that should count toward this total, and any published literature on medical marketing's return on investment is largely based on observational data and cannot be fully relied upon.

The two coauthors previously served as medical experts in testosterone litigation and were cofounders of a company that provided data about the benefits and harms of prescription drugs, which ceased operations in December 2016. No other conflicts of interest were reported.

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SOURCE: Schwartz LM et al. JAMA. 2019 Jan 8. doi: 10.1001/jama.2018.19320.

Continued from previous page

verse community of physicians; we want to retain as many people in the field as possible, and we want them to feel supported," she said.

Beyond asking all GME-sponsoring institutions to adopt parental leave policies, Dr. Magudia believes trainees must be better informed. "It should be clear to training program applicants what the policies are at those institutions," she said. "That information is extremely difficult to obtain, as we've discovered. You can imagine that, if you are the applicant, it can be difficult to ask about those policies during the interview process because it may affect how things turn out."

In the second study, Briony K. Varda, MD, of the department of urology at Boston Children's Hospital, and her colleagues also noted the complications of balancing parental leave with training requirements from specialty boards. They compared leave policies among American Board of Medical Specialty member organizations and found that less than half specifically mentioned parental leave for resident physicians (JAMA. 2018 Dec 11;320[22]:2374-7).

Dr. Varda and her colleagues reviewed the websites of 24 ABMS boards to determine their leave policies; 22 had policies but only 11 cited parental leave as an option for residents. Twenty boards have time-based training requirements and allow for a median of 6 weeks leave for any reason; none of the boards had a specific policy for parental leave. In addition, only eight boards had "explicit and clear clarifying language" that would allow program directors to seek exemptions for their residents.

Though limitations like not detecting all available policies – and a subjective evaluation of the policies that were reviewed – could have affected their study, the coauthors reiterated that the median of 6 weeks leave is less than the average leave for faculty physicians. They emphasized the detriments associated with inadequate parental leave, including delayed childbearing, use of assisted reproductive technology, and difficulty breastfeeding.

Dr. Varda underlined the issues that arise for program directors, who "must weigh potentially conflicting factors such as adhering to board and institutional policies, maintaining adequate clinical service coverage, considering precedent in the program, and ensuring that resident physicians are well trained." Use of competency-based rather than time-based training milestones to determine certification eligibility could lessen the stresses for new-parent residents, she noted.

The researchers disclosed no relevant conflicts of interest.

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SOURCES: Magudia K et al. JAMA. 2018 Dec 11;320(22):2372-4; Varda BK et al. JAMA. 2018 Dec 11;320(22):2374-7.

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