Advances in the Treatment of Crohn’s Disease and Ulcerative Colitis

Inflammatory bowel disease (IBD) is a chronic inflammatory disease that can cause progressive functional and structural damage to the gastrointestinal tract. IBD is a global disease with increasing prevalence. In this article, Mayo gastroenterologists provide an overview of new treatment approaches for Crohn’s disease (CD) and ulcerative colitis (UC).

Treat-to-target approach
Medical therapies for IBD have traditionally focused on symptom control. While the use of oral aminosalicylates and corticosteroids can be effective in suppressing the inflammatory process and inducing symptomatic remission, this approach has not been shown to alter the natural history of IBD, reduce incidence of long-term complications or improve long-term patient outcomes. This fact, combined with the availability of other therapeutic approaches that can induce mucosal healing, has led clinicians and researchers to question whether symptom control is the most appropriate therapeutic goal in the treatment of IBD.

According to Edward V. Loftus Jr., M.D., a gastroenterologist specializing in IBD at Mayo Clinic’s campus in Rochester, Minnesota, many experts are now advocating for a paradigm shift that emphasizes mucosal healing, rather than clinical remission, as the primary treatment objective. “Administering therapies directed at mucosal healing that may favorably modify the natural history of IBD when used in a treat-to-target approach is gaining acceptance,” says Dr. Loftus.

Disease severity assessment tools
Dr. Loftus notes that it’s important to recognize that accurate assessment of disease activity and severity in IBD continues to be challenging. Two widely used tools, the symptom-based Crohn’s Disease Activity Index (CDAI) and the Crohn’s Disease Endoscopic Index of Severity (CDEIS), often paint very different pictures of disease activity.

“In patients with Crohn’s disease undergoing treatment with prednisolone, research data shows a complete lack of correlation between the CDAI and the CDEIS,” explains Dr. Loftus. “This suggests that focusing on severity of symptoms alone may be an inappropriate measure of therapeutic efficacy because CD symptoms are insensitive and nonspecific for bowel inflammation.”
The presence of both inflammation and structural bowel damage in asymptomatic patients also underscores the utility of obtaining endoscopic evidence for mucosal healing, or other objective markers of inflammation, to guide therapeutic decisions and to evaluate their efficacy in IBD treatment trials. For patients with small bowel CD, cross-sectional imaging such as computerized tomography (CT) enterography or magnetic resonance (MR) enterography may be a more appropriate modality to assess inflammation, extent and complications.

“A focus on mucosal or radiographic healing reduces the need for steroids, risk of hospitalization and surgery,” says Dr. Loftus, “so treatment algorithms that incorporate endoscopy or enterography results into decision-making may do a better job of achieving long-term remission and reducing complications.”

In addition to a treat-to-target approach, Talha A. Malik, M.D., M.P.H., notes that Mayo IBD specialists are also implementing and encouraging the development of a standardized approach to the management of IBD for CD and UC that is systematic and evidence-based across all specialized IBD practices, clinics and centers. Dr. Malik is a gastroenterologist specializing in IBD at Mayo Clinic’s campus in Arizona. “Our goal is to provide in-depth interpretation of test results, improved understanding of disease phenotype and severity, as well as management options that are consistent and driven by best research evidence.”

New medications
The immunology of IBD is very complex, and drug targeting is complex. Within the United States, four anti-TNF agents are currently approved for the treatment of IBD — infliximab, adalimumab, certolizumab pegol and golimumab. Biosimilars to these anti-TNF agents have also been developed for use within the United States. Two anti-integrin biologics (natalizumab and vedolizumab) have been approved for use in IBD treatment. And ustekinumab, a biologic that targets cytokines interleukin-12 and interleukin-23 (IL-12 and IL-23), has been approved for CD treatment.

According to Michael F. Picco, M.D., Ph.D., the approach to maximizing the effectiveness of these medications often includes therapeutic drug monitoring. Dr. Picco is a gastroenterologist specializing in IBD at Mayo Clinic’s campus in Florida. “Among patients with an incomplete response to a particular medication, measuring serum levels of a drug can help gain insight into whether a dosing adjustment or a switch to another agent is needed,” says Dr. Picco.

Vedolizumab: Approved in 2014 for both UC and CD, vedolizumab blocks migration of leukocytes into the gut via a blockade of α4β7 integrin (the ligand of which is mucosal vascular addressin cell adhesion molecule 1) and can be considered as a first line agent. Due to its gut-selective approach, this drug may be a good choice for older patients or those with a history of immunosuppression or malignancy.

Ustekinumab: Approved in 2016 for CD only, ustekinumab blocks inflammation produced through IL-12 and IL-23. This molecule, too, can be considered a first line biologic agent, for older adults in particular, and for those with a history of immunosuppression or malignancy and those who have already undergone treatment with anti-TNF agents.

Tofacitinib: Approved in 2018, tofacitinib is a selective Janus kinase (JAK) inhibitor and the first oral medication approved for treatment of moderate to severe UC. The Food and Drug Administration examined results from three controlled clinical trials to assess tofacitinib’s efficacy and safety. In two placebo-controlled induction trials — OCTAVE Induction 1 and 2 — tofacitinib outperformed the placebo in achieving remission in patients with UC. Published results for these two eight-week placebo-controlled trials demonstrated that 10 mg of tofacitinib given twice daily induces remission in 17 to 18 percent of patients by week eight. Among responders at week eight, tofacitinib maintained remission in 34 to 41 percent of patients at the end of one year, with steroid-free remission rates that were 30 to 42 percent better than those seen with placebo.

According to Dr. Loftus, multiple other potential drugs are now in the development pipeline, including several molecules that are beginning or more than halfway through phase III trials.

- JAK inhibitors such as upadacitinib and filgotinib are being studied in phase II and III trials of UC and CD. Both of these molecules are selective JAK1 inhibitors, and data from phase II trials demonstrated their effectiveness as treatments for moderate to severe CD.
- Etrolizumab, an anti-β7 integrin, was effective in moderate to severe UC in a phase II trial and so far in an open-label induction trial in phase III. It also looks promising in induction of moderate to severe CD.
- The anti-mucosal addressin cell adhesion molecule (MadCAM) monoclonal antibody (renamed SHP647) was effective in UC but not in CD in phase II trials.
• The anti-p19 (anti-IL-23) antibodies, brazikumab and risankizumab, were effective in moderate to severe CD in phase II trials. Another p19 antibody, mirikizumab, was recently shown in a phase II trial to be effective for moderate to severe UC.
• The oral sphingosine 1-phosphate (S1P) receptor modulator, ozanimod, was effective for moderate to severe UC in a phase II trial and appeared promising for moderate to severe CD in an open-label induction trial. Another S1P receptor modulator, etrasimod, was recently shown to be effective for clinical response, clinical remission and endoscopic response in a phase II trial of moderate to severe UC.

“With multiple agents with different mechanisms of action for our patients with IBD under study, the future looks bright,” says Dr. Loftus.

Advanced Imaging and Endoscopic Tools Enhance Diagnosis and Treatment of PSC and Cancer Surveillance

Primary sclerosing cholangitis (PSC) is a chronic, idiopathic biliary tract disease characterized by inflammation, fibrosis and strictures that can progress to cirrhosis and end-stage liver disease. PSC is progressive and associated with a significantly elevated risk of cancers of the liver, gallbladder, bile ducts and colon. The length of time it takes for the disease to progress can vary. In some individuals, PSC progresses rapidly after diagnosis. Others can go decades without significant progression or symptoms.

The cause of PSC is unclear. A combination of genetic predisposition and immune system factors could be involved. The majority of patients with PSC are male and nearly 80 percent also have inflammatory bowel disease (IBD).

About 50 percent of patients with PSC have no clinical symptoms, and diagnosis occurs after the discovery of elevated liver enzymes during routine bloodwork. Symptoms can include pruritus, right upper quadrant abdominal pain and acute bacterial cholangitis.

Mayo Clinic specialists in gastroenterology and hepatology see a very large cohort of patients with PSC and employ highly specialized endoscopic practices to diagnose and manage this disease and its complications.

High-quality cross-sectional cholangiographic imaging can help confirm the presence of liver and biliary tract abnormalities associated with PSC. Magnetic resonance cholangiopancreatography (MRCP) provides indirect visualization of the bile ducts and the presence of inflammatory strictures, fibrotic biliary tree changes and bile duct dilation, all in a noninvasive and essentially risk-free platform (Figures 1 and 2).

“In most individuals with PSC, MRCP will reveal diffuse biliary changes, including multifocal stricturing within the intrahepatic...
and/or extrahepatic bile ducts, accompanied by upstream dilation,” explains M. Edwyn Harrison, M.D., a gastroenterologist at Mayo Clinic’s campus in Arizona. “About 20 percent of individuals with PSC will present with biliary changes limited to the intrahepatic ducts,” says Dr. Harrison.

The use of endoscopic retrograde cholangiopancreatography (ERCP) as a diagnostic tool has declined now that MRCP is available. “Therapeutic ERCP is appropriate for use in patients who develop pain with abrupt elevations in bilirubin, acute cholangitis or progressive dominant strictures on MRCP,” explains Dr. Harrison.

Dominant strictures typically occur in about half of patients with PSC and can lead to biliary obstruction. “In these patients, therapeutic ERCP is useful for dilation and stent placement in PSC-induced dominant strictures,” says John A. Martin, M.D., a gastroenterologist at Mayo Clinic’s campus in Rochester, Minnesota. “This would include strictures with a diameter of 1.5 mm in the common bile duct or 1 mm in the intrahepatic duct,” says Dr. Martin.

Drs. Harrison and Martin also caution that because complications associated with ERCP include pancreatitis and cholangitis, this procedure should be performed by experienced endoscopists in high-volume centers.

**Cancer surveillance**

Because malignancy causes substantial morbidity and mortality in individuals with PSC, heightened cancer surveillance is recommended. Mayo Clinic endoscopists employ specialized screening tools and evidence-based protocols to reduce the disease burden in this population.

**Cholangiocarcinoma (CCA):** Individuals with PSC have a lifetime risk of CCA ranging from 5 to 20 percent. Current guidelines recommend a serial ultrasound or an MRI/MRCP and CA 19-9 to screen for CCA every six to 12 months.

When used alone, imaging studies don’t provide a high degree of sensitivity and specificity, so Mayo Clinic endoscopists also commonly employ forceps biopsies and fluorescence in situ hybridization (FISH) and cholangioscopy during ERCP to screen for dysplasia or CCA. FISH uses fluorescently labeled DNA probes to identify the presence of chromosomal abnormalities in bile duct cells to enhance diagnostic sensitivity.

“In patients with a dominant stricture identified during imaging, we consider performing ERCP with brush cytology, forceps biopsies and FISH to confirm or rule out the presence of dysplasia or cholangiocarcinoma,” says Dr. Martin.

Authors of a study published in *Therapeutic Advances in Gastroenterology* in 2015 concluded that this triple-modality approach offers improved sensitivity and specificity for the diagnosis of CCA (82 percent) when compared with conventional brush cytology alone or other single-modality testing (27 to 59 percent).

Researchers are also investigating additional markers for CCA with the goal of developing a more sensitive diagnostic screening tool. Some experts believe that specific serum microRNAs, a class of noncoding RNAs involved in gene regulation, could serve as diagnostic and prognostic biomarkers for both PSC and CCA.

**Gallbladder cancer:** Individuals with PSC have a lifetime risk of gallbladder cancer of approximately 2 percent. Mayo staff note that annual imaging with MRCP to screen for the development of CCA is also useful to screen for gallbladder cancer.

**Colorectal cancer:** Individuals with PSC and concomitant IBD are at increased risk of colorectal carcinoma. Mayo Clinic IBD specialists recommend surveillance colonoscopy annually to screen for any precancerous or cancerous colon lesions. Chromoendoscopy is often considered in these patients to increase the sensitivity for detecting premalignant dysplasia, especially in patients who have previously had indefinite dysplasia.

**Liver transplantation**

About 40 percent of individuals with PSC will eventually require a liver transplant. Transplantation can be considered for individuals who develop evidence of decompensated cirrhosis and those with PSC-related complications, including refractory pruritus or recurrent cholangitis.

In the past, a diagnosis of unresectable hilar CCA was considered a contraindication for liver transplantation due to frequent recurrence and poor long-term survival. In 1993, Mayo Clinic developed a novel therapeutic protocol combining neoadjuvant chemoradiation and orthotopic liver transplantation to treat patients with unresectable hilar CCA or CCA arising in the setting of PSC.

A report authored by Mayo Clinic transplant specialists and published in *HPB (Oxford)* in 2008 demonstrated that the combination of neoadjuvant therapy, operative staging to rule out regional metastases and liver transplantation has achieved remarkable success for selected patients with early-stage hilar CCA.
“Our liver transplant program remains one of the few centers nationwide that performs transplants on these patients,” notes co-author Gregory J. Gores, M.D., a transplant hepatologist at Mayo Clinic’s campus in Rochester, Minnesota.

Summary
Advanced endoscopic techniques performed by experienced endoscopists can enhance the diagnosis and management of PSC, and aid in surveillance for hepatobiliary malignancy. When combined with neoadjuvant chemoradiation, orthotopic liver transplantation can be used to treat patients with unresectable CCA associated with PSC.

For more information


Nonpharmacological Approaches to Management of Functional Gastrointestinal Disorders — Where Are We Now?

Adult functional gastrointestinal disorders (FGIDs) are brain–gut interaction disorders that affect about 1 out of every 4 adults and have a significant negative impact on quality of life, work productivity and health care costs.

Irritable bowel syndrome (IBS) is one of the most common forms of FGIDs and is estimated to affect 1 out of 7 adults in the United States. This disorder is characterized by continuous or recurrent abdominal pain or discomfort associated with altered bowel habits, with no evidence of an organic disorder (such as an ulcer or a blockage), a structural abnormality or another cause for chronic GI symptoms when testing (such as bloodwork, X-rays or endoscopy) is performed. There are three distinct subtypes of IBS, which are categorized based on bowel habits: constipation-predominant (IBS-C), diarrhea-predominant (IBS-D) and mixed-type (IBS-M).

In this article, Mayo gastroenterologists discuss the Mayo Clinic experience and recent research findings related to the use of dietary interventions and other nonpharmacological measures in managing IBS and other types of FGIDs.

Dietary measures
The majority of individuals with IBS note that symptoms begin or worsen after eating a meal. Individuals with diarrhea-predominant IBS experience an exaggerated gastrocolonic motor response to ingestion of food that causes postprandial pain and rectal urgency. Although individuals with IBS do not commonly have true food allergies, sensitivities to foods are reported by nearly half of patients. A growing number of studies have examined the role of dietary factors in IBS and suggest that dietary modifications might help prevent or reduce symptoms.

Fiber supplementation: Supplementation with a soluble fiber preparation, such as psyllium, is still regarded as an effective initial approach to the management of constipation-predominant IBS. Providers should have patients increase the dose gradually, while reminding them that it may take up to 12 weeks for evidence of results. Brian E. Lacy, M.D., Ph.D., and co-authors affirmed the efficacy of dietary fiber in managing IBS in an American College of Gastroenterology monograph on IBS management published in The American Journal of Gastroenterology in 2018. Dr. Lacy is a gastroenterologist at Mayo Clinic’s campus in Florida. “The low cost and lack of significant side effects make soluble fiber a reasonable first line therapy for IBS patients,” says Dr. Lacy.

Probiotics: Multiple randomized controlled trials have established that probiotics have beneficial effects on global symptoms, and on bloating and flatulence in individuals with IBS. Adil E. Bharucha, M.B.B.S., M.D., a gastroenterologist at Mayo Clinic’s campus in Rochester, Minnesota, co-authored a comprehensive review article about FGIDs associated with abdominal pain published in Mayo Clinic Proceedings in 2016. In a discussion about the role of dietary measures, Dr. Bharucha and co-authors note that although Bifidobacterium infantis improves abdominal pain and reduces defecation difficulty significantly, it does not affect stool frequency or consistency.

Gluten and FODMAPs: Gluten and fermentable oligosaccharides, disaccharides, and monosaccharides and polyols (FODMAPs) have recently gained attention as a possible dietary trigger for IBS symptoms. FODMAPs are short-chain carbohydrates present in stone fruits, legumes, lactose-containing foods and artificial sweeteners.

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In an article published in The American Journal of Gastroenterology in 2018, Dr. Lacy and co-authors share the results of a systematic review and meta-analysis of randomized controlled trials (RCTs) examining the efficacy of gluten-free diets (GFDs) and low-FODMAP diets as a treatment for IBS. These diets are among the most common diets recommended by health care providers to improve IBS symptoms.

The researchers analyzed two RCTs of a GFD in 111 participants, and seven RCTs that compared a low-FODMAP diet with various control interventions in 397 participants. This review concluded that these trials provided insufficient evidence that a GFD or low-FODMAP diet was effective in reducing IBS symptoms.

According to Dr. Lacy, the evidence supporting the use of a GFD was not statistically significant. “Our analysis noted that these trials were relatively small, subject to a high risk of bias and that, overall, the evidence was low in quality according to GRADE criteria. The three RCTs that compared a low-FODMAP diet with rigorous control diets had the least heterogeneity between studies, but also the least magnitude of effect,” says Dr. Lacy.

Some researchers have expressed concern that restricted diets could cause problems with prolonged use. These problems might involve nutritional deficiencies or unforeseen changes in the colonic microbiome. While more data is needed on this topic, Dr. Lacy notes that one study presented at the ACG 2017 Annual Scientific Meeting produced some interesting results. The study compared the impact of low-FODMAP diets and modified National Institute for Health and Care Excellence (mNICE) diets on IBS symptoms over a four-week period and concluded that the low-FODMAP diet may be associated with major micronutrient inadequacies.

Despite the limitations of the available study data about the efficacy and safety of specific dietary modifications, many experts believe that working with patients to monitor their diets and make dietary modifications still has value. But Dr. Lacy cautions that dietary modifications should be undertaken with care. “Given the limited studies and lack of long-term data, we need to provide careful advice and, ideally, use a multidisciplinary team approach that includes a dietitian,” says Dr. Lacy.

Mayo FGIDs specialists recommend having patients keep a detailed log of daily dietary intake, to aid in identifying particular foods that aggravate symptoms. Clinicians can consider an initial trial of an individual dietary intervention if certain foods (such as fructans or gluten) appear to be triggers. Patients who continue to have persistent symptoms while a trial is underway, or patients who can’t identify any possible triggers, can try a four-week trial low-FODMAP diet with the consultation of a dietitian. The dietitian can help tailor the specific therapy to each individual and create menus that comply with any dietary restrictions.

In partnership with investigators at Arizona State University, Mayo Clinic gastrointestinal motility thought leaders are conducting research on the physical role of the gut microbiome and the gut-brain axis in FGIDs. Ongoing research efforts are addressing the interplay of nutrients and the gut microbiome, and assessing the impact of treating gut dysbiosis to search for ideal dietary and supplemental recommendations for patients on their journey to wellness.

**Psychological and behavioral approaches**

**Effective patient-physician relationship:**

Dr. Bharucha notes that establishing an effective patient-physician relationship is important, because many individuals with functional GI disorders feel abandoned and undertreated and seek care from multiple doctors with limited success. “We need to approach these patients with empathy and provide reassurance through appropriate testing that their condition is not life-threatening. We also need to educate them about the disease, set reasonable expectations for treatment and engage them in managing their condition.”

Dr. Bharucha and co-authors note that life experiences during childhood and adulthood, lack of social support, and other social factors can lead to maladaptive earned-illness behaviors and predispose some individuals to functional GI and psychiatric disorders. This means that a history of verbal, sexual or physical abuse or major life stressors such as bereavement or divorce may factor into the management of FGIDs in some patients (Figure).

**Psychological and physical interventions:**

Individuals with a history of life stressors may benefit from psychological and behavioral interventions, tailored to the symptoms, functional impairment, psychological distress and symptom expression. The goals of these interventions include pain management, improvement in daily function and relief from psychological distress. Dr. Bharucha and co-authors noted that a meta-analysis of 41 trials involving 2,290 patients observed that psychological therapy is moderately effective for improving IBS symptoms for up to one year after therapy.
“Cognitive behavioral therapy can help patients relax, provide a sense of control over symptoms and induce more parasympathetic activity,” explains Dr. Bharucha. “Diaphragmatic breathing exercises can help patients reduce belching, regurgitation and vomiting.”

According to Tisha N. Lunsford, M.D., a gastroenterologist at Mayo Clinic’s campus in Arizona, a variety of personality traits, including neuroticism, emotional hypersensitivity, maladaptive stress, coping and aggression, have been shown to be associated with poorer health care quality of life and therapeutic outcomes following both psychological and pharmacological treatments. Dr. Lunsford co-authored a 2010 article in *Clinical Gastroenterology and Hepatology* that explores this dynamic in patients with FGIDs.

“Our results confirmed our primary hypothesis that a clinically meaningful subset of patients with FGIDs test positive for the Type D personality trait,” explains Dr. Lunsford. “Consideration of personality traits may allow for improved risk stratification in research and in planning treatment for these individuals.”

Various psychological and physical therapies appear to be safe and effective in FGIDs but may not be widely available. Led by integrative medicine practitioners at Mayo Clinic’s campus in Arizona, physicians, nurses, dietitians, psychologists, physical therapists, acupuncturists and massage therapists, as well as instructors in movement classes such as yoga and tai chi, are committed to providing therapies that have been researched and have scientific evidence to support them.

“For more than a decade, Mayo Clinic physicians have been integrating complementary and alternative therapies with conventional care to meet the emotional, spiritual and psychological needs of the patient and to complement addressing physical symptoms,” explains Dr. Lunsford. “Integrative medicine reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health care professionals and disciplines to achieve optimal health and healing.”

**For more information**


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Mayo Clinic Gastrointestinal Cancers 2019: Current and Emerging Strategies in Multidisciplinary Care
March 14-16, 2019, in San Diego
This course includes presentations on the treatment of the whole spectrum of gastrointestinal cancers, including esophageal, gastric, hepatocellular, pancreatic, small bowel, bile duct, anal and colorectal, and gallbladder.

Gastroenterology & Hepatology Board Review 2019
Sept. 5-8, 2019, in Chicago
This course is designed for candidates preparing for certification and maintenance of certification (MOC) examinations in gastroenterology and hepatology and includes relevant topics such as pathology, endoscopy, radiology and nutrition.

5th Annual Gastroenterology and Hepatology Update 2019
Oct. 5, 2019, in Phoenix
This course includes information on the diagnosis and management of multiple disorders, including esophageal cancer, eosinophilic esophagitis, anti-coagulation, obesity, acute pancreatitis, gastrointestinal cancer, cirrhosis and portal hypertension, cholestatic and autoimmune liver disorders, hepatitis, and controversies in liver transplantation.

7th Annual Mayo Clinic Esophageal Diseases Course 2019
Dec. 6-7, 2019, in Phoenix
This course explores significant advances in diagnosis, therapy and identification of new diseases, including high-resolution manometry and impedance monitoring, new techniques in endoscopic detection and treatment of Barrett's esophagus, and insights into new diseases such as eosinophilic esophagitis. The program includes a hands-on workshop for interpretation and performance of motility studies, new endoscopic imaging techniques, endoscopic mucosal resection and ablation, and transnasal endoscopy.