Advanced Diagnostic Testing Essential for Intestinal Motility Disorders

Perhaps one-third or more of patients with gastrointestinal (GI) symptoms have a motility or functional GI disorder. Although conventional wisdom holds that these disorders lack a well-defined pathophysiology or specific therapy, Adil E. Bharucha, MBBS, M.D., at Mayo Clinic in Minnesota, notes that a careful clinical assessment integrated with the results of refined diagnostic tests is extremely useful for effectively managing these patients.

Many of the tests used to evaluate bowel disorders discussed below were pioneered or validated through extensive research at Mayo Clinic, and many are only available at Mayo.

Gastrointestinal scintigraphy
A noninvasive, radionuclide imaging test with broad clinical indications, scintigraphy measures gastric emptying (Figure) and small bowel and colonic transit. At Mayo Clinic, a unique version of this test provides a screening assessment of gastrointestinal motor function within 24 to 48 hours. The results of the test provide the basis for sophisticated and more-refined intraluminal assessments of gastric and small intestinal or colonic motility. For example, gastroduodenal manometry is used to diagnose gastric dysmotility or intestinal pseudo-obstruction while colonic barostat testing may disclose severe colonic motor dysfunction that may be amenable to surgery. On the other hand, a majority of patients referred to Mayo Clinic with a diagnosis of gastroparesis are found to have normal stomach emptying when transit scintigraphy is performed properly.

Single photon emission computerized tomography (SPECT)
This radionuclide test uses 3-D images to calculate stomach volume before and after a sample meal and is the only noninvasive approach to quantify gastric accommodation. Impaired gastric accommodation may explain upper GI symptoms such as early satiety and is potentially amenable to specific drug therapy.

High-resolution anorectal manometry (HRM)
High-resolution anorectal manometry (HRM) is increasingly used to assess anorectal function in clinical practice. Until recently, however, normal values had not been established, limiting identification of abnormal values. Dr. Bharucha and colleagues recently found that contrary to common belief, a majority of young, healthy women have a negative anorectal gradient, which limits the utility
of a negative gradient with HRM to diagnose defecation disorders. Mayo Clinic investigators have used HRM and magnetic resonance defecography to identify phenotypes in constipation and fecal incontinence. These results can be very useful in directing therapy, such as pelvic floor rehabilitation in patients with a defecation disorder.

Pelvic floor magnetic resonance imaging (MRI)
MRI provides detailed images of the pelvic floor that help diagnose defecation disorders and organ-specific prolapse without exposure to ionizing radiation. Mayo Clinic is one of only a few centers offering specialized pelvic floor retraining for patients with refractory constipation due to pelvic floor dysfunction.

Motility Interest Group
In 2012, the Motility Interest Group at Mayo Clinic in Minnesota saw nearly 1,700 new and established patients. Dr. Bharucha notes, “Patients come here because we offer a multidisciplinary approach with many specialists working together seamlessly, access to refined diagnostic tests, informed approach to the latest pharmacotherapy, use of psychological therapies, skilled pelvic floor therapists, experienced laparoscopic surgeons, and the willingness and ability to deal with especially challenging problems.”

Endoscopic Sleeve Gastroplasty
Safe, Effective for Weight Loss

The worldwide incidence of obesity and associated metabolic comorbidities has more than doubled since 1980. In the United States, one-third of adults have a body mass index (BMI) greater than 30. For many of them, bariatric surgery is the only modality offering clinically significant and sustained weight loss.

But high-cost, high-risk bariatric procedures will not be able to meet the current burden of disease, especially for people with mild to moderate obesity, according to Barham K. Abu Dayyeh, M.D., and Christopher J. Gostout, M.D., both of Mayo Clinic in Minnesota.

“Most patients will need something more effective than medications but not as invasive as surgery, and endoscopy is well-positioned to assume that role,” Dr. Abu Dayyeh says. “We know that altering various segments of the intestinal tract in gastric bypass can induce changes in neurohormonal signals, leading to improved satiety, increased metabolism and reduction, if not resolution, of diabetes. In endoscopy, we now have the tools to replicate some of those benefits.”

One of the most promising endoscopic weight-loss procedures is transoral sleeve gastroplasty, which uses an endoscopic suturing device to mimic surgical sleeve gastrectomy. Creating an endoscopic vertical gastroplasty reduces stomach capacity by 80 percent while avoiding the micronutrient deficiencies associated with gastric bypass surgeries.

Although it is reversible, sleeve gastroplasty is not intended to be temporary. Dr. Gostout likens the procedure to orthodontics — a lifelong process requiring a series of periodic interventions, in this case to address suture integrity and increased meal capacity.

Mayo Clinic researchers recently completed a small pilot feasibility study of endoscopic sleeve gastroplasty. The results, published in the September 2013 issue of Gastrointestinal Endoscopy, demonstrated safety and feasibility. A second trial studying the procedure’s metabolic effects is underway.

“Our first six patients experienced about a 30-pound weight loss at six months, representing a 36 percent reduction in excess body weight — a loss has been maintained up to one year,” Dr. Gostout says, adding that rapid weight loss is an effective trigger for better lifestyle choices.

“People see they are losing weight and are motivated to follow their diet and initiate exercise, which are essential.”

Endoscopic sleeve gastroplasty is an outpatient procedure, patients resume their normal lifestyle in a day or two, and side effects are minor. The cost is roughly one-third that of bariatric surgery.
Mayo Clinic also offers qualified patients endoscopic revision after a bariatric procedure through reduction of the gastrojejunal stoma diameter and gastric pouch size.

“The procedure can take patients who have gained some weight back to the same level of restriction they felt after the initial surgery,” Dr. Abu Dayyeh says. “Our patients average a 25-pound weight loss over six months.”

For more information

Complex perianal fistulas, which may affect up to 40 percent of people with Crohn’s disease, can have a profound impact on quality of life. Yet the limitations of current treatments make multidisciplinary management of this condition extremely challenging. In many patients, the ideal goal — complete and sustained fistula closure — is never achieved, and recent improvements in medical and surgical therapies have not solved the problems of poor wound healing, recurrence and incontinence.

“Over the years, different approaches have been used to fill and cover the defective tissue and allow it to regrow in a healthy way, but most of these approaches have failed,” notes Eric J. Dozois, M.D., associate program director for general surgery at Mayo Clinic in Rochester, Minn. For instance, initial reports demonstrated high success rates for bioprosthetic fistula plugs — a finding not borne out in subsequent studies.

Dr. Dozois explains, “It’s hard to have a standardized cohort with the same biological environment, so there are many factors that may complicate the data, but once more centers used the plug and published the data, no one could match the original 70 to 80 percent success rate. Actually, there is about a 30 percent chance that a plug, in and of itself, will be successful in the first two years. So, though plugs are exciting and encouraging, they didn’t quite get us there.”

In the past decade, however, another approach — cell therapy, in which stromal cells are cultured and expanded to produce autologous adult stem cells — has emerged as a compelling option for wound healing in a variety of settings. In trials involving treatment of fistulizing Crohn’s disease, the cells are injected around the fistula opening and directly into the fistula tract. Early studies in Europe and Asia have demonstrated sustained complete closure in a majority of treated patients.

“Stem cells give the body’s own immune response a boost; it’s a turbo-charged approach to healing,” Dr. Dozois says. “We can’t heal fistulas with surgery; all we can do is control infection and make sure things aren’t getting
out of hand. Stem cells offer a way to rebuild, reconstruct, regenerate.’’

But Dr. Dozois’ enthusiasm for stem cells does not extend to the current method for delivering them. ‘‘Injecting stem cells is like throwing darts at a dartboard. It occurred to me we could try impregnating a fistula plug with the cells and so deliver them more directly.’’

Now, a phase I trial is underway at Mayo Clinic in Minnesota that proposes to do exactly that: determine the safety of adipose-derived mesenchymal stem cell transfer using a biomatrix in fistulizing Crohn’s disease. It is the first study to do so.

Study sponsor, William A. Faubion, M.D., notes, ‘‘Previous studies were done in the setting of fibrin glue. We wanted to grow the cells on a matrix, which turned out to be synthetic. The cells wouldn’t stick to the porcine intestine plug, but they loved the synthetic one.’’

Allan B. Dietz, Ph.D., co-directs Mayo Clinic’s Human Cellular Therapy Laboratory, which has been developing stem cell technologies for various clinical indications for more than six years and will provide cells for the current study.

“We are a group of clinicians and translational scientists interested in bringing cells as drugs to patients,’’ Dr. Dietz says. ‘‘We have spent six years preparing cells for clinical use, not studying them in mice. These studies are very hard to get funded, but we have a group of private donors who have enabled things like this to happen.’’

**Trial design**

Mayo investigators hope to enroll 20 patients with perianal fistulizing Crohn’s disease in the study. Each will undergo standard adjuvant therapy, including infection drainage and placement of a draining seton. After six weeks, the seton will be replaced with a fistula plug containing 20 million autologous mesenchymal stem cells, which have been cultured and expanded from a small fat biopsy collected from each patient.

Patients will be followed for fistula response and closure for 24 months. Short-term success is defined as complete closure at three months and long-term success as sustained closure at one year.

Dr. Dozois says, ‘‘If this is successful, patients will no longer have recurring infections or have to undergo multiple operations ultimately leading to a permanent diversion. That is the impact this could have. If damaged tissue can be reversed, remodeled or replaced, then we no longer have to crudely remove parts of people’s bodies. This approach allows us to try to rebuild what was originally there.’’

He adds, ‘‘The important message for patients and referring physicians is that we are studying and developing new regenerative therapies and may have something definitive in a year or two. If patients can hang on and not undergo major surgeries, there may be a solution just around the corner.’’

Dr. Dietz concurs, saying, ‘‘This is the last big frontier in medicine. First there was surgery, then drugs. Now regenerative medicine comes to the fore as we begin to understand the ability of the body to heal itself.’’

**For more information**

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Multimodality Approach Improves Odds in Pancreatic Cancer

Despite improvements in overall survival for most cancers, survival for patients with pancreatic cancer has remained dismal for decades. For all stages of pancreatic cancer, the one- and five-year survival rates are 20 percent and 4 percent, respectively.

The main cause is late detection and tumor spread, which affects 50 percent of patients at diagnosis. Other tumors are unresectable because of vascular encasement. Only 20 percent of patients have tumors confined to the pancreas at diagnosis.

According to Mark J. Truty, M.D., a surgical oncologist at Mayo Clinic in Minnesota, surgery is the one aspect of pancreatic cancer care that has improved significantly over time. But the technical refinements and advances in postoperative care that reduced complications and operative mortality have not improved survival — patients with resectable cancers have an average survival of just 18 to 20 months, with overall five-year survival rates of 20 to 25 percent.

“We can do complex cancer operations, including advanced reconstructions of veins and arteries, quite safely, but with no essential impact on long-term outcomes. For every technical improvement developed, there is decreasing incremental improvement in overall survival,” Dr. Truty explains. “As the majority of patients develop metastatic disease after curative operations, it is painfully obvious that most probably have undetectable metastases at the time of surgery.”

To address unseen cancer cells and improve long-term outcomes, Mayo Clinic recently began using the combination regimen FOLFIRINOX for neoadjuvant therapy. In a recent phase III trial for patients with metastatic pancreatic cancer, FOLFIRINOX had a more than threefold greater response rate compared with gemcitabine.

**Figure.** Graph of U.S. patient five-year survival for various cancers (all stages combined). Although only 12th in incidence, pancreatic cancer ranks as fourth-leading cause of cancer death in the United States. Data obtained from SEER 2003-2009.
The first pediatric liver transplant at Mayo Clinic was performed in 1985. Since then, Mayo surgeons have performed transplants on 126 young patients for various indications, including biliary atresia — the primary indication for transplantation in children — and a broad range of cholestatic, metabolic and autoimmune liver diseases.

Dr. Truty, too, is seeing significant response rates in patients — some with borderline or locally advanced tumors. Those patients also receive radiation before surgery to avoid a positive margin.

This strategy has many benefits. It identifies patients who have chemotherapy-resistant micrometastases at diagnosis, thus saving them from unnecessary surgery. It downstages cancers that are otherwise inoperable or at risk of having positive margins. And it allows patients to receive treatment to eradicate known metastatic cancer cells before surgery and gives them time to physically prepare for a major operation.

“We are looking for no metastases, regression or nonprogression of the primary tumor, a biomarker response, and improvement in clinical symptoms. Patients who fulfill these criteria and go to surgery do markedly better than average,” he says. “Margin rates are improved, lymph node involvement is less, and in many cases, there is very little tumor left.”

For these patients, aggressive surgery with multiple vessel reconstruction is worth it, Dr. Truty says, because chances of a positive outcome are much improved. “Before it was a game of chance. Now we are trying to strategize and perform the right operation on the right patients. We stack the odds for our patients and offer hope.”

He adds, “We offer a protocol-based approach. Although each patient and cancer is different, we limit variability to maximize outcome. That helps us push the envelope surgically, to take previously unresectable patients and get them through complex procedures. This is a really exciting time in pancreatic cancer surgery. We now have effective chemotherapy, improved radiation and advanced surgical techniques for a multimodality team approach.”

He notes that patients work with a care team that includes surgeons, oncologists, dietitians and psychologists. The short-term data is very promising.

“We are trying to slow the cancer down and find the right time to intervene surgically. Before, we were basically trying to catch running water with our hands. With this new approach, we are trying to slow the flow from the faucet and in many cases actually freezing the water to make cancer easier to treat.”

## Mayo Clinic Modern Approach to Pancreatic Cancer Surgery

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### Living-Related Pediatric Liver Transplants Expand Transplant Options

The first pediatric liver transplant at Mayo Clinic was performed in 1985. Since then, Mayo surgeons have performed transplants on 126 young patients for various indications, including biliary atresia — the primary indication for transplantation in children — and a broad range of cholestatic, metabolic and autoimmune liver diseases.

With refinements in surgical techniques and advances in anti-rejection medications, outcomes for children have steadily improved; experienced centers now demonstrate an overall survival of 95 percent at one year. But the increased number of transplants has far outpaced the number of available donor organs. In
In late 2013, the Food and Drug Administration (FDA) approved two new oral therapies, sofosbuvir and simeprevir, for hepatitis C virus (HCV) infection. Both are expected to offer higher viral response rates with less toxicity and shorter treatment durations than the protease inhibitors boceprevir (Victrelis) and telaprevir (Incivek), approved in 2011.

Sofosbuvir is a nucleotide analogue NS5B polymerase inhibitor — the first in this class to receive FDA approval. In combination with pegylated interferon alfa 2-a and ribavirin, it is approved for use in treatment-naive patients with chronic genotype 1 HCV infections, the most prevalent form. Combined sofosbuvir and ribavirin have been endorsed for genotype 2 and 3 infections.

Simeprevir, an NS3/4A protease inhibitor, is used with interferon and ribavirin for HCV genotype 1 patients, with or without concurrent HIV infection, who are treatment-naive or have failed interferon therapy. In phase III trials, 80 percent of treatment-naive patients and 79 percent of relapers on the three-drug combination had undetectable virus levels at 12 weeks compared with 50 and 36 percent of controls, respectively. Most adverse events were related to interferon and ribavirin, but some, including rash, pruritus, photosensitivity and nausea, were associated with simeprevir.

Although the new regimens for genotype 1 patients have higher response rates and may be better tolerated, they are still interferon based, notes John J. Poterucha, M.D., a viral hepatitis expert at Mayo Clinic in Minnesota. “The goal of recent investigations has been to develop oral regimens that don’t include interferon or ribavirin and we’re on the way. I think an interferon-free regimen will be available in the next year or two,” he says, while adding a note of caution.

“Patients listed for transplants are less tolerant of medications, and many of these studies didn’t include them. So although this is a sea change for hepatitis C treatment, HCV-associated cirrhosis is likely to remain the most common indication for liver transplantation because the sickest patients can’t tolerate treatment or their disease is too advanced.”

New antiviral regimens are likely to benefit those with less severe disease, however, especially given the U.S. Preventive Services Task Force recommendation that asymptomatic adults born between 1945 and 1965 be offered a one-time screening for HCV infection. This is in addition to long-standing screening recommendations for injection drug users and others at high risk.

“It’s thought that widespread screening will identify about 75 percent of all cases of HCV.
and do so more effectively than targeted screening,” Dr. Poterucha explains. “But it’s going to take some time to implement that process and incorporate it into mainstream health care.”

In the meantime, hepatologists with expertise in evaluating and managing HCV infection, including the use of newer drugs, are available to see patients at all three Mayo Clinic sites — Arizona, Florida and Minnesota.

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Upcoming CME Courses

**Mayo Clinic Gastroenterology & Hepatology 2014**
March 13-16, 2014, Loews Portofino Bay Hotel, Orlando, Fla.
Designed for physicians and other health care providers in gastroenterology and hepatology, this course discusses new approaches to the diagnosis and management of gastrointestinal and liver diseases.

11th Annual Course: 2014 Mayo Clinic EUS Summit and Principles and Pearls in Pancreatology
July 30-Aug. 2, 2014, Rochester, Minn.
Designed to provide endosonographers, gastroenterologists and other health care providers at all levels of experience a comprehensive multidisciplinary review of endoscopic ultrasound.

**Gastroenterology & Hepatology Board Review**
September 2-7, 2014, The Westin Chicago River North, Chicago
This board review course is designed to simulate board examinations in gastroenterology. The program will include relevant topics such as pathology, endoscopy, radiology and nutrition.

**Mayo Clinic Gastroenterology & Hepatology 2015**
Designed for physicians and other health care providers in gastroenterology and hepatology, this course. Discusses new approaches to the diagnosis and management of gastrointestinal and liver diseases.

For information on CME courses, visit www.Mayo.edu/cme/gastroenteroly