MAYO CLINIC

Clinical Update

Focus on Gastrointestinal Medicine and Surgery

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INSIDE THIS ISSUE

Endoscopic Advances Improve Outcomes, Speed Recovery, Usher in Era of Scarless Surgery

As a center of endoscopic excellence with a robust research-based clinical practice, Mayo Clinic is leading endoscopic innovations. Three clinical highlights of these advances are direct endoscopic necrosectomy; natural orifice transluminal endoscopic surgery (NOTES); and endoscopic treatment of Barrett's esophagus.

Acute Pancreatitis and Direct Endoscopic Necrosectomy

Severe acute pancreatitis is life-threatening. It frequently requires stays in intensive care units for days or weeks and often disrupts the pancreatic duct. Over several weeks solid necrotic pancreatic tissue collects, intermixed with pancreatic juice. If this collection becomes infected or becomes large enough to cause outlet obstruction, drainage is warranted.

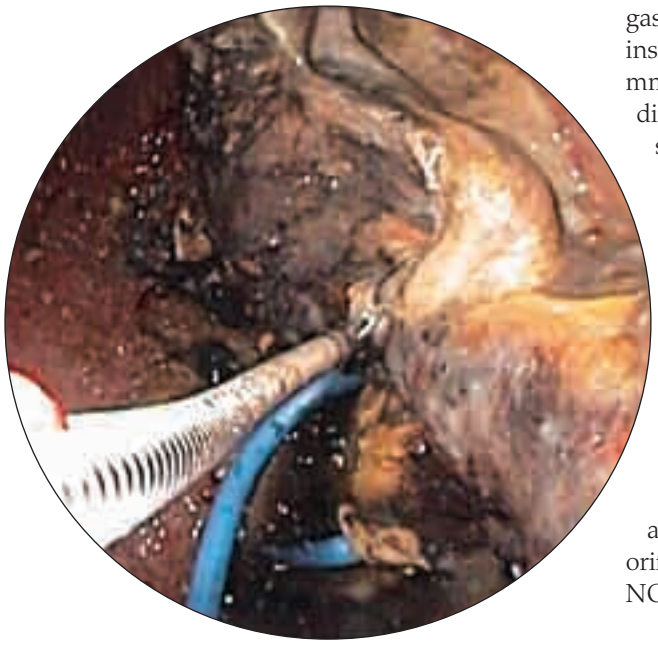


Figure 1. *The endoscope is passed directly into the cavity to debride the solid material, depositing it in the stomach or duodenum.*

Conventional treatment is an open or, more recently, laparoscopic necrosectomy to drain the cavity and debride the solid material. Open surgical drainage has notable drawbacks.

"Often a very large and difficult operation is required, because the area that needs debridement is located behind the stomach and multiple operations may be required. The patient is often left with large scars, external drains, and subsequent fistulas," explains Todd H. Baron, MD, an interventional endoscopist and director of pancreaticobiliary endoscopy at Mayo Clinic in Rochester, Minnesota. "We knew there had to be a better way."

By 2005, a Mayo Clinic team refined a nonsurgical approach that is in use today—direct endoscopic necrosectomy. The Mayo team passes an endoscope inside the stomach or the duodenum and then "punches" through the gastric or duodenal wall to create a tract to the inside of the cavity. The tract is enlarged up to 20 mm in diameter. The endoscope is then passed directly into the cavity (Figure 1) to debride the solid material, depositing it in the stomach or duodenum for normal evacuation.

Between 3 and 5 procedures are typically needed to eliminate all the necrotic material. The first procedure is usually performed in the hospital, with 1 day of observation. Subsequent debridements are performed as outpatient procedures.

NOTES for Scarless Surgery

In fall 2009, the gastrointestinal endoscopic surgical team ushered in a new era of surgery at Mayo Clinic: scarless, pain-free, natural orifice transluminal endoscopic surgery, called-NOTES (see sidebar, page 2).

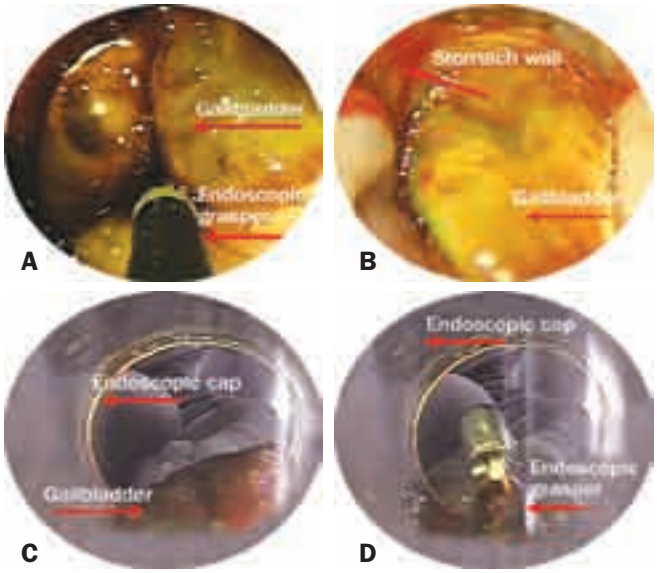


Figure 2. *Specimen retrieval after NOTES transgastric cholecystectomy A, The gallbladder is grasped. B, The gallbladder is pulled into the gastric lumen and up the esophagus. C, The gallbladder is removed from the body through the mouth and grasped by the surgical assistant. D, The endoscopic grasper releases the gallbladder specimen to the assistant.*

NOTES eliminates the skin wounds of open and laparoscopic procedures by using natural anatomic passages for access, such as the vagina and anus, and by working with a new generation of endoscopic tools. Two new NOTES protocols have been approved by the Mayo Clinic Institutional Review Board: transvaginal cholecystectomy and emergency repair of ulcers. The transvaginal cholecystectomy will be introduced first (Figure 2).

Research into the tools, techniques, and physiologic responses has been ongoing for years. NOTES clinical trials are now enrolling patients, according to gastroenterologist Christopher J. Gostout, MD, of Mayo's Developmental Endoscopy Unit. Dr Gostout also is director of training and technology for the American Society for Gastrointestinal Endoscopy.

Explains Dr Gostout: "At Mayo Clinic we are fortunate to have the Developmental Endoscopy Unit for advancing NOTES. This specialized unit has allowed a range of surgical subspecialties to interact in cadaver laboratories and on animal models—including surgeons from gynecologic oncology, urology, and general surgery, as well as research engineers. We feel we have a 'dream team' of multidisciplinary expertise."

Todd H. Baron, MD, Christopher J. Gostout, MD, and Kenneth K. Wang, MD

The Appeal of NOTES

NOTES procedures have been done experimentally at several advanced centers in Europe and the United States with encouraging results.

- Blood pressure metrics indicate NOTES is less stressful on the body than the transabdominal procedure to which it was compared.
- Patients are strongly attracted to the generally pain-free aspect of NOTES. NOTES penetrates visceral organ tissue rather than the pain-sensitive body wall, as is done in traditional procedures.
- Patients like improved cosmesis and rapid recovery after NOTES, which leaves no incisional scars.
- NOTES procedures can be performed anywhere. They do not require a sterile operating room because there is no skin wound involved, and this may be a major economic incentive for the development and adoption of NOTES.

Barrett's Esophagus: Toward Nonincisional Treatment of Cancer

Esophageal adenocarcinoma arising from Barrett's esophagus is increasing faster than any other cancer in the United States, and the tumors are lethal, with 90% of patients dying within 5 years of diagnosis (Figure 3). Etiology is linked to the common problem of gastrointestinal reflux. Traditionally open surgical esophagectomy has been the treatment of choice for patients with Barrett's esophagus with early cancers and high-grade dysplasia. Recently, Mayo Clinic gastrointestinal specialists have come to favor endoscopic therapies. Endoscopic mucosal resection is now routinely performed on an outpatient basis at Mayo, and data demonstrate that it is a highly cost-effective, less invasive, and tissue-sparing approach for cases of early cancer. This allows gastroenterologists to obtain tissue and staging. Published results show it offers equivalent outcomes to open surgery.

"The endoscopic approach is an effective outpatient alternative management strategy for high-grade dysplasia and early-stage cancer.

We have almost 4 years' worth of cancer follow-up data that show approximately equivalent outcomes. We think these patients can be much better treated endoscopically, with much less trauma, time, and expense," explains Kenneth K. Wang, MD, director of the Barrett's Esophagus Unit at Mayo Clinic and expert in endoscopy therapies for this disorder.

The Mayo Clinic team is advancing management of Barrett's esophagus through such technically demanding innovations as removing larger and more deeply penetrating tumors. In the past, elevated tissues were the surgical target. Today, Mayo Clinic performs more flat tissue removal than any other US center. Its success with endoscopic removal of cancers and high-grade dysplasia is leading to creation of a full-thickness resection. Endoscopic submucosal dissection, which has been used successfully in Asia, is also being investigated.

Figure 3. *Tumor arising from Barrett's esophagus. Recently, experienced gastrointestinal specialists have come to favor endoscopic treatment with excellent results.*

Specialty Hepatobiliary Clinics Provide Optimal Outcomes, Eliminate Fragmented Care, Implement Unique Advances

Most cancers that arise in the liver and biliary tract are carcinomas, and the different stages at which they present require highly specialized care. Because of the biological and clinical complexity of these malignant lesions, patients with hepatocellular carcinoma (HCC) are most likely to obtain positive outcomes by seeking care at medical institutions with high-volume HCC experience and advanced expertise.

"At Mayo Clinic, we have the diagnostic and treatment breadth, depth, and expertise in the multidisciplinary care of all patients who have benign and malignant tumors," explains Gregory J. Gores, MD, chair of the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota. His research focus is hepatobiliary malignancy.

"Often HCC is diagnosed at an advanced stage and/or is complicated by the underlying liver disease; hence, it is often not amenable to curative therapies. Because there are limited options for chemotherapy, comprehensive specialty centers such as ours play a crucial role as innovators in improving long-term outcomes," adds his Mayo colleague, HCC researcher Lewis R. Roberts, MBChB, PhD.

Access to Excellence

Mayo Clinic's Hepatobiliary Neoplasia Clinic provides a single site for patients to access coordinated care. From initial evaluation to diagnosis, medical therapy, minimally invasive or open surgery, transplantation, and aftercare, patients benefit from the unified approach of a specialty clinic.

Gregory J. Gores, MD, and Lewis R. Roberts, MBChB, PhD

Novel Therapy for Nonresectable Tumors

The best patient outcomes are achieved in early-stage HCC through liver transplantation and surgical resection. Local ablative and locoregional therapies can also be effective early-stage options. They include percutaneous ethanol injection, radiofrequency ablation, transarterial chemoembolization, and transarterial radioembolization.

For nonresectable disease, Mayo Clinic is one of the few centers in the United States to offer novel intra-arterial radiotherapy known as transarterial radioembolization. A minimally invasive technique, radioembolization relies on the injection of radioactive (yttrium 90) microspheres into the hepatic arteries that supply the tumor. Once injected, the microspheres selectively implant in tumor arterioles where they emit low-dose radiation targeted to the tumor, which is lethal to the tumor cells. Radioembolization is highly challenging to perform safely and produces best outcomes when performed by experienced teams.

Bile Duct Cancer

Mayo Clinic physicians have long been pioneers in the diagnosis and management of cholangiocarcinoma. Mayo is now expanding its leadership in the field by improving diagnosis of bile duct cancer with the advanced cytologic technique of fluorescence in situ hybridization (FISH).

Routine cytology analysis relies on visually identifying abnormally shaped cancer cells under a microscope. FISH improves visual detection of malignant cells through the use of fluorescent probes that attach to the DNA of cells and then become brightly visible under a fluorescence microscope. Because cancer cells have an abnormal DNA structure, on FISH analysis, cancer cells show extra copies of the fluorescent probes when compared with normal cells (Figure).

In a recent paper published in the journal *Gastroenterology*, the Mayo research team reported that the combination of cytology and FISH raised the detection rate of bile duct and pancreatic cancer from 20% to 43%.

Beyond advances in diagnosis with FISH, Mayo remains a leader in the treatment of biliary disorders. Among its areas of expertise are the use of endoscopy to relieve jaundice and the development of a new treatment protocol employing liver transplantation for patients with biliary tumors.

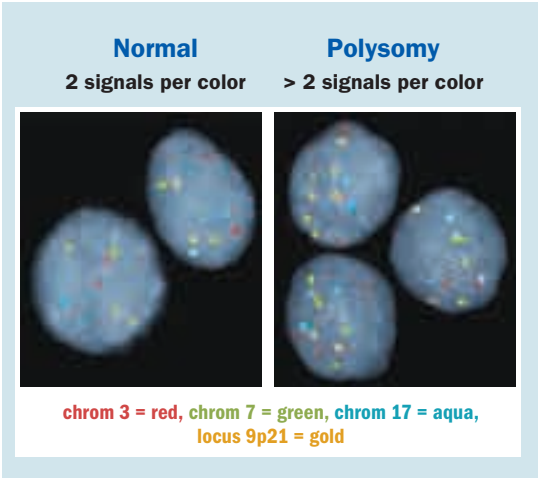


Figure. *Cancer detection is improved by identifying a normal bile cell vs a polysomy (cancerous) cell through use of fluorescence in situ hybridization (FISH) technique. Mayo Clinic practitioners were among the first to use advanced cytologic techniques in combination with FISH to improve diagnosis of bile duct cancer by analyzing chromosome copy number. Left, FISH panel showing normal bile cells. Right, Panel showing how FISH analysis improves diagnosis by improving visibility of cancer cells as revealed through increased chromosome copy number.*

Successful Inflammatory Bowel Disease Management With Minimally Invasive Surgery, Biomaterials, and Clinical Trials

Robert R. Cima, MD, and Edward V. Loftus Jr, MD

Ulcerative colitis and Crohn's disease are the most common clinical presentations of inflammatory bowel disease (IBD), affecting more than 1 million Americans. Recent advances at comprehensive IBD centers are creating better and more stable management options for both diseases.

IBD specialists at Mayo Clinic in Rochester, Minnesota, provide care for more than 5,000 IBD patients a year and internationally are at the forefront of improving care. Explains Robert R. Cima, MD, a Mayo Clinic colorectal surgeon and vice chair for quality and safety in Mayo Clinic's Department of Surgery: "Successful IBD treatment requires a well-coordinated team of experts working on many fronts: skin and wound care, nutrition, use of newer medications such as biologics, and expertise in understanding these new agents' impact on the timing of surgery. In medically refractory cases, the team collaborates with surgeons in deciding the best next step. At advanced centers, this involves mastering the technological innovations of multiple minimally invasive approaches."

Adds Edward V. Loftus Jr, MD, a Mayo Clinic specialist in IBD who serves as an associate editor of *Inflammatory Bowel Diseases* and was an associate editor of the *American Journal of Gastroenterology*: "The development of new medical therapeutic agents such as the biologics is really transforming the treatment of IBD. Mayo is a leader in helping assess their effectiveness through clinical trials, new measures, and new technologies, such as imaging with magnetic resonance enterography."

Ulcerative Colitis Advances

Up to 30% of ulcerative colitis patients require surgery at some point in the course of their disease. To meet these needs, Mayo Clinic refines and

Figure. *Figure. A, Preoperative photograph of a woman with advanced Crohn's disease who presented in 2007 with complex enterocutaneous fistula. B and C, Reconstruction of abdominal wall using biomaterial. D, Completed reconstruction. E, The same patient at follow-up 1 year later in 2008, showing durability of the repair and experiencing exceptional recovery: body weight of 103 pounds and tolerating regular diet and oral electrolyte replacements.*

pioneers multiple minimally invasive surgical techniques. For example, in a study of 12-month postoperative functional outcomes of ileal pouch-anal anastomosis procedures, results were equivalent after open surgery and minimally invasive surgery (33 patients in each treatment group). Advantages of minimally invasive surgery include reduced pain and scarring; decreased hospital length of stay from about 7 to 10 days to about 3 to 5 days; and lowered risk of intrahospital complications such as urinary tract infection and pneumonia.

Another recent study determined the short-term safety and feasibility of a minimally invasive total proctocolectomy with Brooke ileostomy for refractory ulcerative colitis. Using Mayo Clinic's prospective IBD database, the research team analyzed results of 44 procedures to determine 30-day safety results. The team concluded the approach is a safe, feasible option for select patients.

Crohn's Disease Advances

Crohn's disease is a highly complex, incurable disease that is extremely heterogeneous in presentation. Mayo Clinic offers comprehensive treatment for all aspects of the disease, producing results that improve patients' quality of life. When surgery is required, the goals are to preserve as much intestine as possible and to minimize the need for a stoma.

Medically refractory enterocutaneous fistulas and herniated stomas often develop in patients with complex Crohn's disease (Figure). Mayo Clinic surgeons have successfully used new biomaterials such as human acellular dermal matrix to help reconstruct the abdominal wall after partial resection. The Mayo team concluded the biomaterial is safe and effective.

Additional Mayo Clinic contributions to improving the care and treatment of patients with Crohn's disease include transforming management of the disease by helping create a new index of disease activity. Using objective measures and evidence of bowel destruction from enterographic imaging studies, Mayo researchers are helping overcome weaknesses of the current symptom-based index for Crohn's disease severity. It is considered too subjective and unreliable by many as a guide for prescribing the powerful new biologic agents. Mayo also leads US participation in a large multicenter international clinical trial to develop a new objective marker of bowel damage, the International Program for New Indices in Crohn's Disease. For more information about it, contact Brenda Becker 507-538-7872.

In addition, Mayo Clinic clinical researchers are participating in clinical trials and assess results of new biologic therapies. These therapies include immunomodulators to reduce inflammation. Patients who are naïve to or who have failed anti–tumor necrosis factor (anti-TNF) therapies may be eligible for these trials. The biologic agents include ustekinumab (anti-interleukin 12/23), vedolizumab (anti-alpha4-beta7-integrin), and golimumab (anti-TNF). For enrollment information, contact Denise Dahle at 507-284-0535.

Retraining Pelvic Floor Muscles to Correct Medically Refractory Chronic Constipation

Adil E. Bharucha, MBBS, MD

Up to 50% of patients with chronic constipation have pelvic floor dysfunction (PFD, or dyssynergia). This condition is characterized by impaired coordination between pelvic floor (eg, puborectalis) relaxation and abdominal wall motion, which is necessary for normal defecation. However, PFD is not widely recognized as a possible cause of chronic constipation. As a result, many patients with medically refractory constipation do not receive optimal therapies that enable them to recover normal bowel habits.

Biofeedback Therapy and the Bowel

When mechanical, anatomic, and disease- and diet-related causes of constipation have been ruled out, clinical suspicion should be raised to the possibility that PFD is causing or contributing to constipation. Informed by an understanding of PFD, best-practices treatment of medically refractory chronic constipation due to PFD includes retraining the pelvic floor muscles with biofeedback.

Based on the principle of operant conditioning, biofeedback helps patients modify bowel habits by restoring defecation, which normally entails propulsive forces coordinated with relaxation (see sidebar, page 7).

"Many patients with refractory chronic constipation have unrecognized PFD, which improves with biofeedback therapy. PFD is an underrecognized cause of chronic constipation. Patients are most likely to be evaluated for PFD when they seek care at an advanced multidisciplinary center and to receive biofeedback therapy in this setting," explains Adil E. Bharucha, MBBS, MD, a gastroenterologist and specialist in PFD at Mayo Clinic in Rochester, Minnesota.

Multidisciplinary Approach

Mayo Clinic gastroenterologists address chronic constipation through an integrated, multidisciplinary approach. When chronic constipation is a presenting symptom, a careful digital rectal examination is indicated. Its purpose is to evaluate such features as high anal resting tone and inability to relax the puborectalis muscles.

Depending on digital exam findings, patient evaluation may also include

- anorectal manometry with 12 circumferential sensors for high-resolution output to assess anorectal pressures (Figure)
- pelvic MRI to visualize pathologic pelvic floor motion and anal sphincter anatomy
- evacuation proctography (defecography) to provide a video recording of pelvic floor motion and anorectal anatomy under various patient conditions (at rest, during coughing, squeezing and straining to expel barium from the rectum)

The methods used to conduct these tests were developed, in part, at Mayo Clinic. Interpretation is guided by an extensive database of normal values, which is important since anorectal functions are influenced by patient age and sex. Test results also are interpreted in the context of each patient's clinical features.

Absent other pathologies, data showing lack of coordination of propulsion and relaxation due to inability to

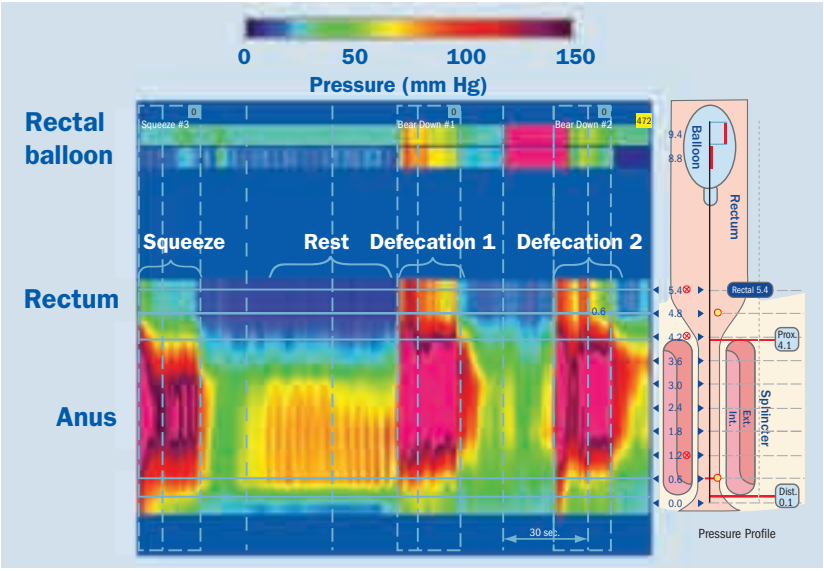
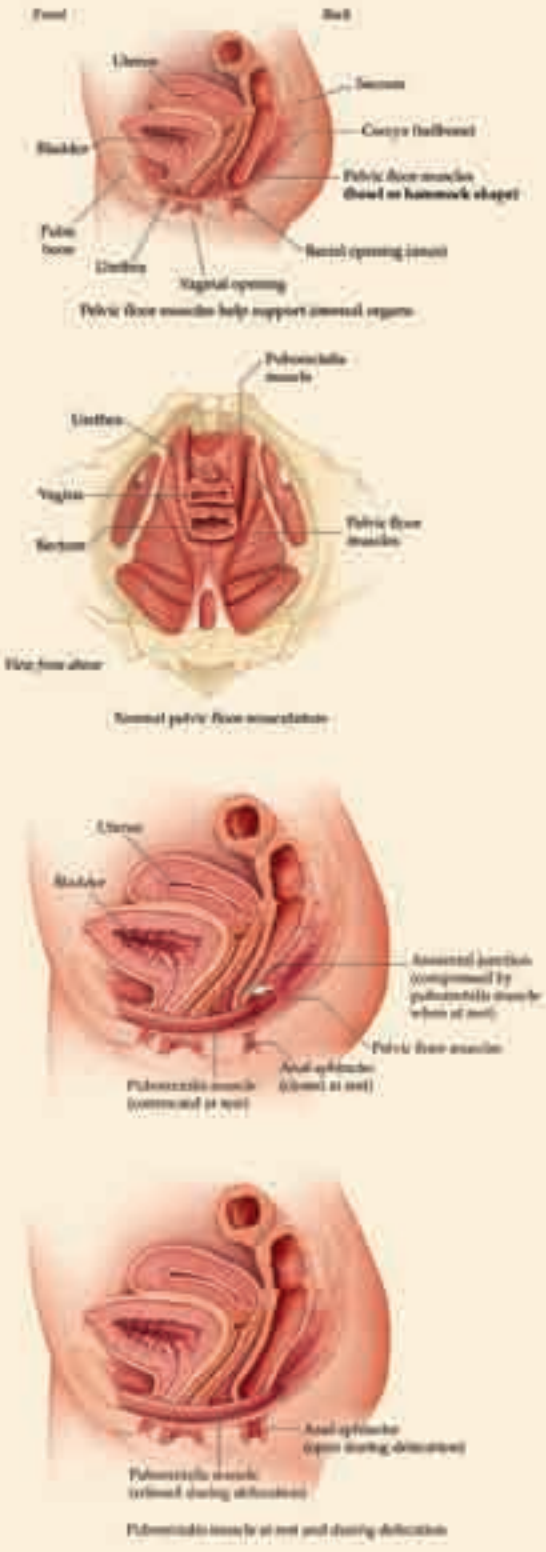


Figure. *High-resolution anorectal manometry reveals pressures and anatomic detail through topographic plots that aid clinicians in understanding causes of constipation and prescribing optimal treatment. In this patient with PFD, anal contraction was observed not only during squeeze but also paradoxically during simulated defecation.*

relax pelvic floor and abdominal muscles are generally the basis for initiating biofeedback therapy. Notes Dr Bharucha: "A majority of patients are delighted with the improvement in symptoms after retraining, which is conservative and safe. Many have suffered for months or years through inappropriate treatments because the central role of PFD in chronic constipation was not recognized and treated."

Outpatient Program



Biofeedback Treatment of Constipation

Biofeedback treatment for constipation at Mayo Clinic consists of an intensive 2-week outpatient program to teach patients how to coordinate the abdominal muscles with those of the pelvic floor for successful evacuation.

Treatment sessions are held Monday-Friday for 2 weeks, during which patients meet with Mayo physical medicine and rehabilitation specialists as follows:

Week 1

- Average of 3 sessions lasting 30 to 45 minutes every day.
- Insertion of a rectal sensor that monitors muscle tension through electromyography (EMG). The EMG activity is visually displayed for the patient to indicate tension and relaxation of the pelvic floor.
- Verbal explanation and cueing from the therapist on what pelvic floor relaxation feels like and how to relax these muscles. Simultaneous visual feedback strengthens learning by showing improvements in relaxation.
- Learning to identify the internal sensations associated with day-to-day relaxation (baseline relaxation) and how to sustain that point.
- Education on the negative effects of both pelvic floor and general tension. Relaxation training may be augmented with the help from occupational therapists who teach diaphragmatic breathing.

Week 2

- Average of 2 sessions each day.
- Insertion of a rectal balloon inflated with varying volumes of water to simulate a bowel movement. The patient learns to sustain relaxation with rectal volume present, to coordinate abdominal activation with dynamic pelvic floor relaxation, and to avoid habit co-contraction of the pelvic floor. The goal is unpressured release of the rectal balloon to simulate normal defecation.
- Teaching long-term skills and exercises for home use to maintain pelvic floor relaxation.
- Education regarding normal bowel function, identification of problematic toileting habits, and behavioral modification.

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Mayo Clinic Gastroenterology & Hepatology 2010

February 22-26, 2010, Westin Kierland Resort, Scottsdale, AZ

Course directors at all 3 Mayo Clinic campuses have joined efforts to design this premier course. Gastroenterology and Hepatology 2010 is designed to update physicians on new approaches to the diagnosis and management of gastrointestinal and liver diseases. Presentations will include general hepatology, motility and nutrition, inflammatory bowel disease, pancreatic disease, endoscopy, and miscellaneous topics. New technologies and endoscopic procedural approaches to specific diseases also will be discussed. Course faculty are thoughtful and conscientious educators and will focus presentations on clinical applications in daily practice. Optional afternoon educational activities, including "Meet the Professor" breakout sessions and an Endoscopy Hands-On Workshop at Mayo Clinic's Center for Procedural Innovation, will be offered. $75 discount for online registration. Course syllabus available online for review prior to the course.

Contact: http://www.mayo.edu/cme/gastroenterology.html, cme@mayo.edu, or 480-301-4580

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See Medical Professionals page for more physician

Welcome to the first issue of Physician Update e-mail newsletter. This newsletter will offer access to articles from the Clinical Update print publication, plus other items of general interest to a physician audience.

Patient Care

Inpatient Video-EEG Monitoring for Epilepsy

Continuous video-EEG monitoring (inpatient) helps localize seizure focus, determine seizure type, and quantify the number of seizures in patients with intractable recurrent seizures and those with an unconfirmed seizure diagnosis.

Optimizing the Functional Performance of Cancer Survivors

There is a growing understanding of the importance of exercise and rehabilitation for cancer survivors. Physical Medicine specialists can help patients manage the negative long-term sequelae of cancer and its treatments and obtain a more satisfying, high-quality recovery.

New Endoscopic Treatment for Severe Gastrointestinal Bleeding

Endoscopic ultrasound-guided therapy appears to be a safe and effective treatment for patients with severe gastrointestinal bleeding for whom conventional therapies have failed. The therapy involves injecting various agents directly into the source to


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