

NEW YORK-PRESBYTERIAN Digestive Diseases

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Surgeons Seek Solutions to NAFLD

Nearly 30 million people in the United States have some form of nonalcoholic fatty liver disease (NAFLD), and more than 8 million of these have nonalcoholic steatohepatitis, placing them at risk for further complications such as cirrhosis and fibrosis, according to physicians. Now, Columbia researchers at NewYork-Presbyterian Hospital are actively studying the causes and treatment of both simple and more active fatty liver disease.

NAFLD, which can arise in the absence of sustained alcohol consumption and usually appears in the setting of obesity, diabetes, and elevated cholesterol levels, is generally not progressive, and may even resolve spontaneously in some cases, according to Paul D. Berk, MD. Indeed, only a small fraction progresses to cirrhosis and liver failure. However, this small fraction is still large enough to explain why NAFLD has become the third major indication for liver transplantation, noted Dr. Berk.

Additionally, the condition is present in about half of obese children, said Paul J. Gaglio, MD. "When they come into adulthood, there will be significant concern regarding progression to more advanced liver disease," he added. As yet, researchers don't know of a generally effective medical treatment for the condition.

"Certainly, weight loss is a good target to aim for, but most medical approaches to this ultimately fail," said Dr. Berk. "And most adults are very

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Hospital Researchers Explore New Therapeutic Options for Hepatorenal Syndrome

Thanks to their involvement in a multicenter, multinational study, Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are at the forefront of investigation into a new treatment option for patients diagnosed with hepatorenal syndrome (HRS), a troubling manifestation of advanced chronic liver disease.

"Until recently, the exact mechanism that led to HRS and the treatment were unknown," noted Samuel H. Sigal, MD. "Over the past 4 or 5 years there has really been an explosion of information as to what causes the condition and how to treat it."

Now, researchers from across the country are leading a clinical trial designed to study the efficacy and safety of terlipressin, a long-acting vasopressin analogue, in

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A patient showing signs of ascites. The hepatic scarification caused by hepatorenal syndrome causes portal hypertension with ensuing ascites.

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Bariatric Procedures and Protocols Set New Standards for Postoperative Care

The surging popularity of bariatric surgery for morbid obesity necessitates postsurgical care with individualized and attentive follow-up by surgeons, due to the risk of nutritional deficiencies and associated diseases. Some 144,000 bariatric procedures were performed last year alone, but the overall paucity of research on postoperative care has led to major initiatives at one of the largest bariatric surgery centers in the United States—NewYork-Presbyterian Hospital.

According to Jonathan Waitman, MD, each major form of gastrointestinal bypass represents a distinct challenge for physicians and for patients, who need to adjust postoperatively to their changed digestive and absorption capacity of food and medication. Various types of vitamin and nutrient deficiencies are associated with the 3 major procedures.

Gastric bypass (Roux-en-Y), the most popular of the weight-loss operations, restricts food intake but is also partly malabsorptive. Some patients have developed deficiencies in iron, vitamin A, zinc, and selenium. Of special concern is the insidious risk of calcium and vitamin D deficiency, which puts patients at risk for metabolic bone diseases and osteoporosis. Detection may be difficult because when dietary sources are inadequate, the bones give up calcium to maintain blood serum levels.

Weight loss after laparoscopic band surgery is not as great as with gastric bypass. Absorption is not altered with this procedure, where a small pouch is created below the esophagus, so in most cases only a multivitamin is necessary. According to Alfons Pomp,

MD, nutritional deficiencies with the adjustable band are relatively infrequent. However, Michel Gagner, MD, added that they can occur “in individuals who vomit frequently due to a too-tight band.”

The duodenal switch, on the other hand, is a significantly malabsorptive procedure that can cause radical weight loss; therefore, all patients who undergo this procedure need to address nutritional issues. Reserved for the most overweight individuals, the switch reshapes and resizes the stomach and is positioned to bypass about half the small intestine. As fat calories are consequently malabsorbed, so are the fat soluble vitamins A, D, E, and K. A generic supplement with added iron and calcium may be enough, but a vitamin B supplement must also be taken.

Patient compliance can be a serious stumbling block in all forms of gastric bypass postoperative care—for a variety of reasons. Nutritional disorders arise gradually and patients frequently take multiple medications for comorbid disorders. Supplements lost in this complex mix can pose problems over time. “Patients who do well do not have signs of vitamin deficiencies until they’re really deficient,” said Dr. Pomp. “They’re tired of seeing a doctor; their insurance changes; patients move.”

At the Weight Loss Surgery Program at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, Dr. Waitman and his colleagues working in the Comprehensive Weight Control Program specialize in the medical management of weight loss, which “dovetails nicely with the bariatric surgery program because we can tackle this problem from multiple directions,” said Dr. Waitman. But the

growing popularity of the surgery nationwide raises a new magnitude of concern. Dr. Waitman regularly sees patients who have fallen through the cracks of care or whose deficiencies have become difficult to manage.

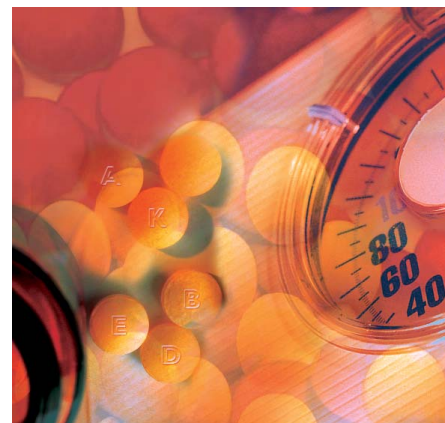
Active probing for signs and symptoms is required, as is a familiarity with the patient’s history and medication profile. “If you don’t know which deficiencies to look for and what they look like, you’re not going to find them,” said Dr. Waitman. Vitamin A-deficient patients may have troubled vision, especially at night. Metabolic bone disease due to calcium and vitamin deficiency may show through fractures. Problems of balance may be related to B12 deficiency, while swelling in the lower extremities may indicate protein/calorie imbalance. Loss of taste sensation is associated with abnormal levels of zinc.

Dr. Gagner added that patients are often burdened with nutritional problems even prior to surgery and in spite of obesity. Vitamin D deficiencies and

Table. Popularity of Bariatric Surgery

Year	Surgeries Performed
2001	47,000
2002	63,000
2003	103,000
2004	144,000
Prevalence of extreme obesity in US (BMI>40)	
1988-1994	2.9%
1999-2000	4.7%

Source: Mitka M. Surgery for obesity: demand soars amid scientific, ethical questions. *JAMA*. 2003;289:1761-1762.



low iron serum levels are common. Some nutritional issues attributed to surgery may in fact have been present preoperatively. "One thing to remember is that nearly 50% of patients seeking weight loss surgery already have vitamin and mineral deficiencies," he pointed out. "They certainly do not look undernourished, but they often eat the wrong type of foods in large quantities."

Indeed, added Louis Aronne, MD, these patients also often require support and counseling services post-op to ensure that they keep the weight off. "A problem we're seeing increasingly is weight regain 3 to 5 years after surgery," he noted. "Some of our patients regain a significant amount of the weight they've lost because they go back to eating soft, high-calorie foods. This can, at least in part, counteract the effects of surgery." According to Dr. Aronne, with some of these patients, physicians at the Weight Control Program have been experimenting with off-label use of certain medications to control weight.

"With dietary counseling and, in some cases, medical intervention," he continued, "we can overcome these problems and get patients back to the lower weight."

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Capsule Endoscopy Identifies Troubling GI Diseases in Children

NewYork-Presbyterian Hospital physicians are expanding the use of capsule endoscopy technology to diagnose gastrointestinal (GI) diseases, from inflammatory bowel disease (IBD) and familial adenomatous polyposis (FAP) to Peutz-Jeghers syndrome, Crohn's disease, and celiac disease, in pediatric patients.

Capsule endoscopy uses a color video imaging capsule to capture images of the GI tract. It was approved by the FDA for use in children 10 years and older in October 2003, although some physicians have used the device in younger patients, according to Robbyn Sockolow, MD.

"In pediatric patients, it depends on the ability to swallow a capsule," she said. "Some 8- to 9-year-olds aren't able to swallow a pill that big." The capsule is 11 mm by 26 mm and weighs less than 4 g.

As with adult patients, children undergoing capsule endoscopy fast the night before the procedure. Once they have ingested the capsule—usually with a glass of water—they wear a lightweight equipment "belt" that is outfitted to record visual images of their GI tract. Pediatric patients are allowed only a clear liquid diet for a few hours immediately after ingestion and a light meal 4 hours later.

"After swallowing the capsule, children can go to the movies, go for a walk, and keep themselves occupied during the day," Dr. Sockolow said. Eight hours later, the patient comes back to the physician's office where as many as 57,000 images are then downloaded from the equipment belt to a computer. The capsule is naturally excreted and disposed of.

"There are many advantages to capsule endoscopy in children," said Dr. Sockolow. "There's no sedation and it doesn't hurt. There's no anxiety about anesthesia or prepping for an invasive procedure."

According to Dr. Sockolow, physicians need to receive proper training on how to properly interpret the downloaded images. Doctors at NewYork-Presbyterian Hospital, for instance, are trained to identify landmarks such as the beginning of the stomach, the start of the small intestine, and the capsule's exit to the colon while looking for abnormalities. Images of anything unusual can be stored in a computer database.

"There's a steep learning curve before you become proficient at reading capsule studies," said Dr. Sockolow. As a result, she added, the procedure should be done in centers such as NewYork-Presbyterian Hospital, where capsule studies are often performed on children.

"If we see something like Crohn's disease in patients, we can shift their management and change medications. We usually don't recapsule patients unless we are looking for therapy endpoints that will help with management."

— Robbyn Sockolow, MD



Image captured by capsule endoscopy. NewYork-Presbyterian Hospital physicians are using capsule endoscopy to diagnose gastrointestinal diseases such as inflammatory bowel disease, familial adenomatous polyposis, Peutz-Jeghers syndrome, Crohn's disease, and celiac disease in children.

Once the images are read, physicians can proceed with making treatment decisions. For instance, the procedure can be useful in determining whether a child's IBD is caused by ulcerative colitis or Crohn's disease. This information is vital in mapping out proper treatment.

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NAFLD

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resistant to major lifestyle and dietary changes." As a result, bariatric surgery has become a popular solution.

The National Institutes of Health is currently sponsoring a multicenter group called "Longitudinal Assessment of Bariatric Surgery (LABS)" and NewYork-Presbyterian Hospital is a participating center. The study will evaluate outcomes of several bariatric surgical procedures with 3 to 5 years of follow-up. NewYork-Presbyterian Hospital will be providing the largest number of cases for this research.

While bariatric procedures are known to help resolve type 2 diabetes, lower blood pressure, and reduce cholesterol levels, there have been relatively few follow-up studies on how they impact fatty liver disease, according to Dr. Berk. Some research has indicated that patients who undergo bariatric surgery see improvements in fatty liver disease a year or more after surgery. Initially, however, the rapid weight loss associated with bariatric surgery can actually worsen fatty liver disease. During the period of 3 to 6 months following surgery, when weight loss is most rapid, an enormous load of fatty acids is dumped from adipose tissue into the bloodstream and flows to the liver, which suggests that a short-term increase in steatohepatitis may occur.

"But this needs to be studied further," said Dr. Berk. "What we do know, from small local studies, is that in good hands

The technology is also useful for diagnosing and monitoring polyps in children with Peutz-Jeghers syndrome, or examining whether polyps in children with FAP have undergone malignant changes. Many times, polyps occur in a part of the GI tract, such as the jejunum, where a traditional scope cannot easily reach.

Additionally, doctors can use the device in children with stunted growth to determine whether celiac disease or Crohn's disease, which can impede their growth, is the cause. Capsule endoscopy may also allow physicians to monitor

the risk-to-benefit ratio for conservative bariatric surgery makes it a highly acceptable way to achieve weight loss, helped by good follow-up in [the] post-operative period."

Additionally, bariatric surgeons involved in the LABS study will be able to provide basic scientists with tissue from the intestinal tract, liver, and adipose tissue of obese patients undergoing surgery.

"We're moving away from studying the physiology of obesity and fatty liver in animal models and will be able to address key biochemical questions in human tissues," explained Dr. Berk.

Studying patients who undergo bariatric surgery will eventually help physicians and surgeons predict which people with simple fatty liver will go on to develop more advanced forms of fatty liver disease, said Dr. Gaglio. Researchers also need to determine whether fatty liver has a negative impact on the natural history of hepatitis B and C and alcohol-induced injury to the liver.

Because surgery may not always be a practical solution to America's growing obesity epidemic, researchers also continue to look for medical approaches to weight loss and fatty liver disease. Medical management of fatty liver has been linked to controlling insulin resistance, noted Dr. Berk. Insulin-sensitizing agents such as metformin may help to ameliorate the condition, but clinical trial results are conflicting. "But, there's enough evidence to warrant further clinical studies," noted Dr. Berk.

In small pilot studies, researchers are

children with celiac disease to ensure that they are complying with prescribed dietary requirements.

"There really needs to be an open-mindedness about the power of information gathered from wireless capsule endoscopy," said Dr. Sockolow.

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evaluating drug-assisted weight loss with agents such as sibutramine and orlistat and whether patients experience improvements in their liver tests, said Dr. Gaglio. Additionally, antioxidant therapies that include vitamin E and the use of long-acting oral antibiotics to help prevent inflammation and fibrosis are being studied in patients with simple fat in the liver, he said.

Better understanding of fatty liver disease will come with increasing knowledge of obesity. NewYork-Presbyterian Hospital/Columbia University Medical Center has one of the country's best basic science programs, which is looking into the various aspects of obesity, including genetics, metabolics, and pathophysiology, according to Dr. Berk. "Twenty-five years from now, we'll be doing a lot less bariatric surgery, and applying other approaches to managing obesity," he said. "With this will come better management of fatty liver disease."

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Case Study: Diagnosing and Treating Esophageal Cancer

The following is an actual patient case from the Division of Gastroenterology at NewYork-Presbyterian Hospital/Columbia University Medical Center.

The Case

An 80-year-old woman complained of increasingly severe heartburn and sought help from her gastroenterologist. Initial endoscopic examination showed a small nodule with tiny ulcerations located in the distal esophagus. Biopsy revealed intramucosal carcinoma arising in Barrett's esophagus. She was referred for endoscopic staging and possible therapy for this lesion at NewYork-Presbyterian/Columbia's Division of Gastroenterology, where she saw Peter D. Stevens, MD.

Endoscopic ultrasound revealed that the lesion was limited to the mucosal layer of the esophagus and there were no adjacent lymph nodes (T1_m, N0). In light of the patient's age, surgery was not an option; endoscopic treatment was the procedure of choice for this early lesion. Endoscopic mucosal resection using the cap technique (EMR-C) safely excised the lesion in 3 contiguous sections without bleeding.

The patient was discharged from the hospital the same day and placed on a liquid diet that was advanced to normal after 2 days. Pathology confirmed that the lesion was present only in the mucosal layer and did not invade the muscularis mucosa. Follow-up 6 weeks later showed no evidence of residual malignant tissue or tumor. The patient will undergo intermittent endoscopic surveillance but will likely not require any further interventions.

Discussion

EMR, used to excise flat lesions

within the upper and lower GI tract, is a new procedure that combines the therapeutic power of endoscopic screening with surgical pathology. Originally developed in Japan for patients with gastric lesions, physicians in the United States and Europe use it to remove sessile colon polyps, while gastroenterologists have adapted the procedure for use in the excision of wide areas of Barrett's esophagus with high-grade dysplasia and in early stage esophageal cancer limited to the mucosa and submucosa.

Before the development of this technique, patients with these lesions had to undergo esophageal resection. Although that surgery was life-saving for patients who needed it, the availability of an organ-sparing procedure is a great boon to patients with early-stage lesions. In addition, esophagectomy is associated with significant morbidity and mortality (1%-2%) that increases with age and comorbid illness. According to Marc Bessler, MD, minimally invasive esophagectomy may be an alternative to traditional surgery for patients with recurrent or more deeply invasive tumors. This innovative procedure, he added, "reduces recovery time and postoperative pain and may reduce complications as well."

In the EMR-C technique used with the patient above, the gastroenterologist employed a specially designed cap fitted onto the tip of a standard endoscope. After identifying and marking the perimeter of the lesion endoscopically, the physician created a safety cushion beneath the lesion by injecting a dilute epinephrine solution into the submucosa. This raised the tissue away from the muscular wall of the esophagus and

Endoscopic ultrasound revealed that the lesion was limited to the mucosal layer of the esophagus and there were no adjacent lymph nodes. In light of the patient's age, surgery was not an option.



increased the safety margin for the patient. Following the injection, suction was used to aspirate tissue into the cap at the tip of the endoscope. A specially designed snare was then used to resect the tissue brought up into the cap. Following the removal of 1 capful, multiple specimens were obtained from adjacent areas to create a wider area of excision of the mucosa.

"The advantage of this technique is that it allows us to remove flat lesions with sufficient margins to be considered a complete resection," said Dr. Stevens.

Charles J. Lightdale, MD, concurred, noting that endoscopic surgery using ablative methods leaves uncertainty as to whether the disease was confined to the mucosa.

"The great advantage of EMR-C over ablative methods is the resulting large pathology specimen extending into the submucosa," he said. "The depth of cancer invasion can be assessed with great accuracy." He added that careful follow-up study of patients treated with EMR-C will be important; however, at present, the accumulating data "continue to look highly promising."

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HRS

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the treatment of patients diagnosed with HRS. Officially entitled "A Double-Blind, Randomized, Placebo Controlled, Multicenter, Phase III Study of Intravenous Terlipressin in Patients with Hepatorenal Syndrome, Type I," the study began in June 2004 and is currently being conducted in centers across the country, including NewYork-Presbyterian Hospital. The study is scheduled for completion in 2007.

"This is the first study in the world that is being done prospectively; everything else that has been done for HRS has been retrospective analysis," said Dr. Sigal. "It is also the first [randomized, placebo-controlled] study for HRS."

"This is an area in which relatively little research has been done," added Robert S. Brown, MD, MPH. "We are very excited to be taking a leadership role in this research. The study marks the ongoing collaboration between the campuses of NewYork-Presbyterian Hospital, as well as between specialists and surgeons here."

Terlipressin was initially developed for use outside the United States in the treatment of patients with portal hypertension manifesting in esophageal variceal hemorrhage. Since 2001, doctors overseas have discovered that administering a combination of terlipressin and albumin to patients with HRS can improve patients' kidney function within 3 to 4 days.

HRS involves the development of renal failure in patients with advanced chronic liver disease (cirrhosis) who have portal hypertension and ascites. In patients with liver failure, the presence of ascites, although treatable, represents a recurring complication of the disease and is a likely indicator that the condition will manifest in HRS, according to Paul J. Gaglio, MD. Research indicates that approximately one third of patients with cirrhosis and ascites will develop HRS during the natural history of the disease.

The purpose of the current study is to evaluate the effectiveness of terlipressin as an alternative to other treatments available for patients with renal failure;



Table. Causes of Ascites in U.S.

Etiology	Percentage of Total cases
Chronic liver disease with cirrhosis	81.4
Malignancy (1° intra-abdominal or metastatic)	10.0
Heart failure	3.0
Tuberculosis	1.7
Nephrogenous (dialysis ascites)	1.0
Pancreatic	0.9
Fulminant hepatic failure	0.7
Lymphatic disruption (Chylous ascites)	0.3
Chlamydia infection (Fitz-Hugh-Curtis)	0.3
Nephrotic syndrome	0.2

these include dialysis and drug treatments (which are often combined). Researchers propose that with the administration of terlipressin, patients may recover normal kidney function without the use of dialysis. "Dialysis is frequently difficult when patients present with very abnormal bleeding parameters," said Dr. Sigal.

According to Dr. Sigal, in order to undergo dialysis, patients may require transfusions of plasma and platelets, and such transfusions increase the risk to

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patients who have both lower blood pressure and higher levels of toxins in their systems as a result of chronic liver disease. Indeed, although neither terlipressin therapy nor dialysis cures the underlying liver disease causing renal failure, researchers note that dialysis merely sustains the patient until a liver transplant becomes a viable option. If successful, the study will help establish terlipressin as an effective "bridge to transplant" that restores and normalizes kidney function in patients with chronic liver disease.

"HRS is a highly fatal disease without transplant," noted Dr. Brown. "Our hope is that our ongoing research will provide us with a bridge to treatment, if not a cure, for those patients awaiting transplants."

Robert S. Brown, Jr., MD, MPH, is Medical Director, Center for Liver Disease and

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