



Advancements Continue in Endoscopic Treatment for GERD

Gatekeeper Study Uses Inert Materials Implanted in Esophagus Wall to Provide Acid Reflux Barrier

By Kenneth Binmoeller, M.D. and Laura Miyashita

New endoscopic treatments for gastroesophageal reflux disease (GERD) offer greater options for the 20 million Americans affected by this disease. Despite the efficacy of drugs, GERD is a mechanical disease and not one of acid hypersecretion. It therefore makes sense to treat the underlying mechanical problem. Unlike surgery, physicians can perform endoscopic treatments without general anesthesia in an outpatient setting. An additional advantage of endoscopy is that treatment can be more safely and easily repeated if necessary. This is an important consideration because studies have shown that surgical benefits for GERD are not long lasting and that patients will eventually have to take medications again to control their GERD after a mean of 10 years.

Currently, three endoscopic approaches for GERD are used:

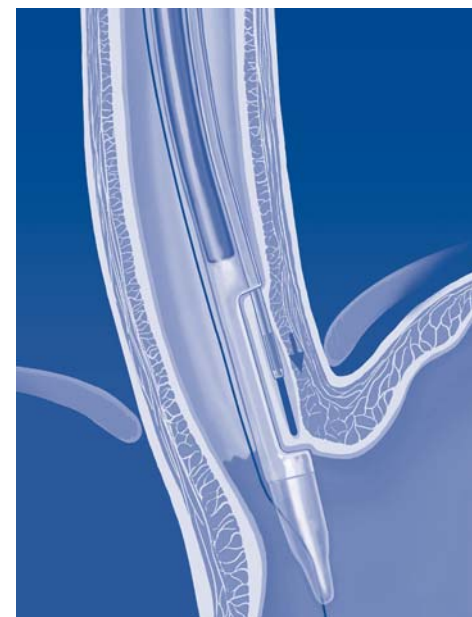
1. **Endoscopic "Sewing Machine"**—In this technique, sutures are placed in the gastric cardia to create an internal plication for inhibiting reflux.
2. **Radiofrequency Current**—The use of such a current causes focal injury to the muscle layer of the

esophagogastric junction and cardia, producing scarification that seems to result in both mechanical and neuromuscular effects which in turn decrease reflux.

3. **Endoscopic Injection or Implantation of Inert Materials**—

Applying materials to the esophagogastric junction is thought to provide a greater barrier to acid reflux.

To further examine the latter approach, California Pacific Medical Center's Interventional Endoscopy Service is recruiting patients for a multi-institutional study to evaluate the efficacy of Medtronic's Gatekeeper™ Reflux Repair System.



Caption here.

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Gastric Neurostimulator Shows Promise for Treatment of Gastroparesis

Enterra Therapy Successfully In Use By 22 Patients at California Pacific

By Shelly Parker, R.N., MSN, ANP-C, Nurse Practitioner, GI Motility

Patients with severe nausea and vomiting associated with gastroparesis who have been implanted with the gastric neurostimulator Enterra™ Therapy have shown favorable results to date, according to California Pacific Medical Center's Director of Motility Services and Study Investigator, William Snape, M.D. As one of eight study sites in the nation for the gastric electrical stimulator (GES), physicians at California Pacific have performed 22 implants to date, including nine in the past year. Nationwide, 1,026 individuals have had Enterra

Therapy implanted since 2000, when the device received humanitarian device exemption from the U.S. Food and Drug Administration.

"The electrical stimulator is a major advance for the treatment of patients with gastroparesis that is intractable to treatment with standard medical stimulants of the stomach," says William Snape, M.D. study investigator. He adds, "Patients with diabetic gastroparesis have had the best response with over 90 percent of these patients having improvement in the gastric emptying and symptoms."

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New Guidelines Surrounding HCV Treatment Duration

Genotype Influences Disease Treatment

By Robert Gish, M.D. and Laura Miyashita

An individual's hepatitis C virus (HCV) genotype plays an important role in treatment decisions, with studies continuing to uncover newer optimal guidelines.

Recent research comparing varying treatment durations with combination therapy (Pegylated interferon and ribavirin) have provided insights that are being put into practice.

"The latest data shows that we should consider customizing therapy to genotype, viral load and one's viral response on treatment," explains Robert Gish, M.D., medical director of California Pacific's Liver Disease Management and Transplant Program. Specifically, according to the latest data, suggested treatment durations are:

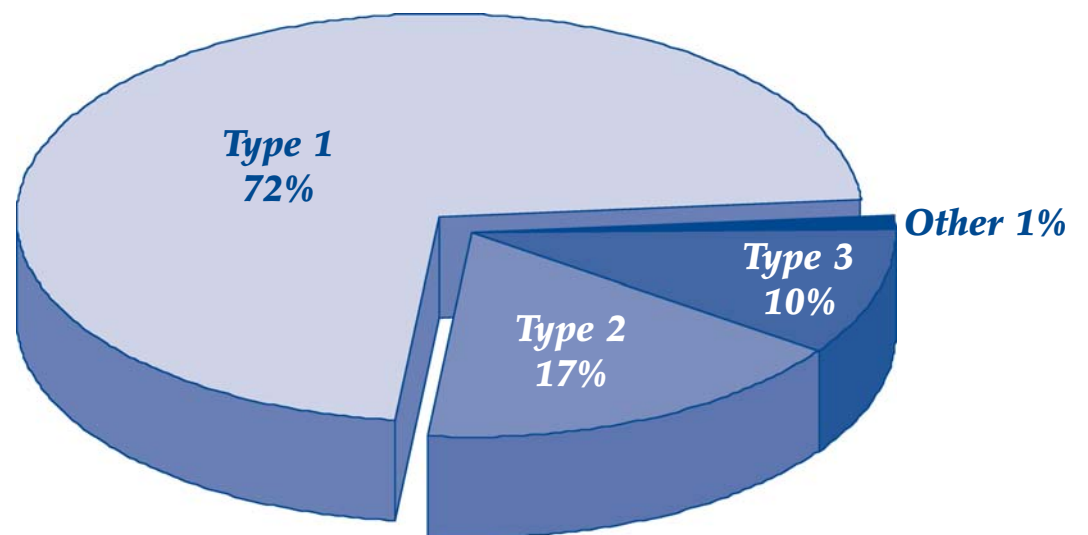
Genotype 1: Treat patient with combination therapy for nine months beyond HCV negative by transcription-mediated amplification (TMA) assay. Minimum treatment of 48 weeks required.

Genotype 2: Treat patient with combination therapy for 14–16 weeks if TMA results are negative at one month. If TMA results still positive at one month, consider 24 weeks of therapy.

Genotype 3: For patients with a viral load <500,000 IU, treat with combination therapy for 24 weeks if TMA negative at one month; if TMA positive at one month, treat with combination therapy for 48 weeks (especially those patients with a viral load over 500,000 IU).

Genotype 4, 5 and 6: Treat patient with combination therapy for nine months beyond HCV negative by TMA assay. Minimum

Distribution of Genotypes in the U.S.



treatment of 12 months required (same as Genotype 1 treatment).

Cirrhosis, HCV/HIV Coinfection, Dialysis Patients and Liver Transplant Recipients:

Treat patient with combination therapy for nine months beyond HCV negative by TMA assay (minimum one year). Dialysis patients should be treated with monotherapy with a PEG IFN. Ribavirin should not be used with these patients except as part of a treatment protocol at a specialized center. Consider maintenance therapy for transplant recipients and other immunosuppressed patients as well as nonresponders with more advanced liver disease.

Acute HCV: Consider monotherapy with interferon for up to six months depending on viral load at the time therapy is initiated.

Genotype Repercussions

To date, physicians have discovered that one's HCV genotype, or genetic structure, does not

influence the natural history of the disease. In all, there are seven different HCV genotypes, but in the United States, genotypes 1, 2 and 3 are most common (see chart). Experience has shown that genotype 1—the most prevalent in the United States—is the most difficult to treat, resulting in lower response rates and the need for a longer treatment duration. Genotypes 2 and 3 are more likely to respond to treatment and require a shorter treatment duration.

The HCV InnoLIPA® or Visible Genetics tests, both distributed by Bayer Corporation, can determine one's HCV genotype and is the standard of care for determine genotype while counseling patients on treatment options. There remains no association between genotype and the chance of developing cirrhosis or liver cancer. The only interesting new association is genotype 3 and fatty liver. Once HCV is cleared in patients with genotype 3, the profound fatty liver seen in these patients can reverse back to normal.

Study Addresses Anemia in Liver Transplant Patients

Erythropoietin Use Shown to Increase Hematocrit in 75% of Patients

By Maurizio Bonacini, M.D. and Laura Miyashita

Anemia, or the lack of red blood cells, is relatively common in patients after liver transplantation. The causes for this have not been studied. To determine methods for controlling anemia in patients who have undergone liver transplantation, physicians at California Pacific Medical Center's Liver Disease Management and Transplant Program recently conducted a study surrounding the use of erythropoietin. Erythropoietin is a naturally occurring hormone that is administered one to two times weekly by subcutaneous injection. The Food and Drug Administration (FDA) has approved erythropoietin for treatment of anemia associated with renal failure, chemotherapy, pre-operative anemia and HIV infection; however, this medication has not been studied for use by liver transplant patients.

The study included 33 patients who had undergone orthotopic liver transplantation (OLT) (of which 82% had hepatitis C) and who had a hematocrit of less than 36%. The average dose of erythropoietin was 34,473 + 10,600 units per week, over the course of about six months. A response to erythropoietin was defined as a 3% increase in hematocrit, which corresponds to about a 10% increase in red cells.

In nearly 75% of patients with post-liver transplantation anemia, erythropoietin increased hematocrit by >3% without affecting white blood cells or platelet counts. Those who responded most favorably had a significantly lower starting hematocrit (29.3% + 3.6%) vs. 34.7% + 6.5%) and lower creatinine levels compared to non-responders. In addition,

the researchers found that patients who were receiving interferon and ribavirin were less likely to demonstrate a response to erythropoietin.

To follow up on these results, investigators Maurizio Bonacini, M.D. and Tami Daugherty, M.D. are starting a small prospective and comprehensive study on anemia and OLT. The goals will be to:

1. Assess the main causes of anemia in that clinical situation; and
2. Assess the efficacy of erythropoietin in correcting anemia and describe its effects on quality of life.

To refer patients for this study at California Pacific's Hepatology Research Center, contact Nata De Vole at 415-600-1110.

Study Focuses on Adults with Liver Disease and Rapid Decline in Renal Function

Recruitment Underway for Phase III Study of Terlipressin

By Laura Miyashita

California Pacific's Hepatology Research Center is recruiting patients with hepatorenal syndrome (HRS) Type 1 to study the safety and efficacy of the drug terlipressin, which has been suggested to improve or reverse this disease by increasing blood flow to the kidneys.

To date, more than 200 individuals with HRS Type 1 have received terlipressin in clinical trials. Research has shown that patients who received terlipressin versus placebo had improved blood flow to the kidney, reduction in serum creatinine and increased urine output.

Study Candidates

Potential trial candidates include any adult patient with chronic or acute liver disease presenting with a rapidly progressive decline in renal function, as evidenced by a doubling of serum creatinine to 2.5 mg/dl or greater within a two-week timeframe. Other causes for renal pathology, such as acute tubular necrosis, obstructive uropathy, septic shock, toxic effects from drugs and hypovolemia must be excluded.

Hepatorenal Syndrome

Hepatorenal syndrome is the development of renal dysfunction in patients with end-stage liver cirrhosis in the absence of any other cause of renal pathology.

According to Study Investigator and Hepatologist Todd Frederick, M.D., "Management of HRS poses a significant challenge to the clinician due to the lack of any approved medications for this disease and the rapidly progressive course it runs. Liver transplantation is the only apparent cure but unfortunately, is unavailable to the majority of these patients. Terlipressin has shown promise in European studies and may provide life-saving time to stabilize patients and potentially allow for more definitive therapy such as transplantation."

For more information on the Terlipressin study or to refer patients, contact Research Coordinator Michelle Murray, R.N., MSN at 415-923-3500 x77338.

Hepatologist Todd Frederick, M.D. Joins Liver Team

By Laura Miyashita

Hepatologist Todd Frederick, M.D. recently joined California Pacific Medical Center's Liver Disease Management & Transplant Program. In this role, Dr. Frederick manages care for both pre- and post-transplant patients. Additionally, Dr. Frederick regularly visits outreach clinics in Chico, Sacramento, Modesto, Redding, Merced and Fresno. Dr. Frederick was previously a fellow in gastroenterology/hepatology at University of California San Diego (UCSD). He completed his internal medicine residency at UCSD and received his M.D. from New York Medical College.

Dr. Frederick has lectured on the management of advanced liver disease, artificial liver support systems and portal hypertension, among other topics. His research interests include the pathophysiology of portal hypertension and clinical management of complications of advanced liver disease. Dr. Frederick is planning clinical trials for hepatic encephalopathy and hepatorenal syndrome (see related article). Dr. Frederick can be reached by phone at (415) 600-1020 or via email at fredertz@sutterhealth.org.

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Implanting the Gastric Electrical Stimulator

At California Pacific, Snape and Surgeons Greg Jossart, M.D., John Feng, M.D. and Paul Cirangle, M.D. work together to evaluate and implant patients with Enterra Therapy. Depending on the patient, the procedure is performed either laparoscopically or with open surgery under general anesthesia. During the procedure, the leads of the stimulator are attached to the stomach wall, 10 cm from the pylorus. The neurostimulator is placed in the abdominal wall's subcutaneous tissue, just below the rib cage. The neurostimulator is programmed in the operating room and turned on one day post operatively. In all, the operation lasts between one to three hours.

Patients stay in the hospital between one to five days and have quarterly clinic visits in the first year following implantation, then annually. At each visit, the stimulator is interrogated and adjusted as needed. Patients fill out an SF-36 V2 to assess quality of life and have gastric emptying studies to assess gastric function.

Indications for Gastric Electrical Stimulation

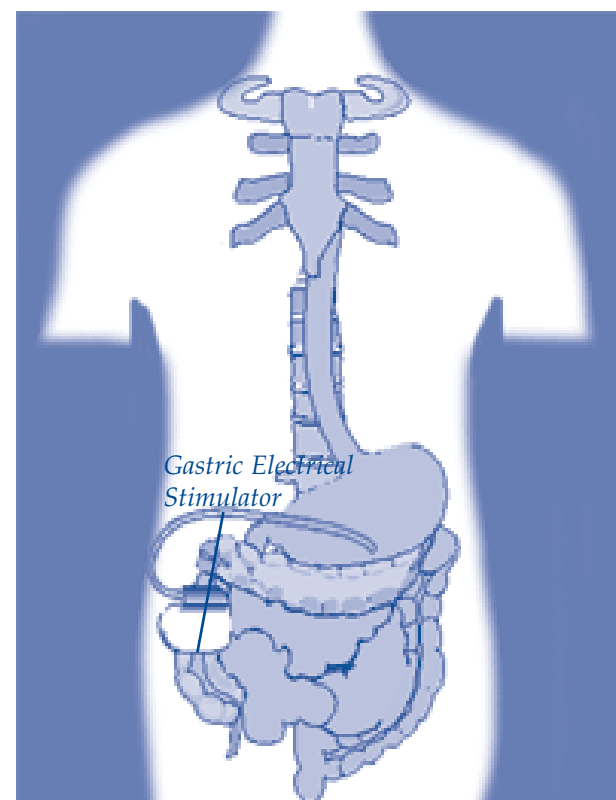
Treatment with gastric stimulation started in 1963 for the treatment of post-operative ileus



Julie Finch had Enterra Therapy implanted in 2004 at age 22 for gastroparesis. She received the implant under the FDA's humanitarian device exemption and reports that she "feels like a normal person again." She plans to return to college in the fall.

and has evolved over the years into a treatment option for gastroparesis. Presently, gastric electrical stimulation is indicated for patients with intractable nausea and vomiting that has been resistant to other therapies. The neurostimulation activates a nausea- and vomiting-control mechanism, using a high-frequency, low-energy stimulation to achieve symptomatic relief. According to WAVESS clinical trial results reported in the August 2003 issue of *Gastroenterology*, gastric electrical stimulation significantly reduced vomiting, improved quality of life and had an acceptable safety profile in a group of 33 patients with long-term gastroparesis.

Tests for gastroparesis include a gastric emptying study, pyloric manometry and antroduodenal manometry, all of which performed at California Pacific's Motility Center. First-line treatments for gastroparesis include diet modification, medications, endoscopic injection of Botox for increased pyloric



pressure, pyloroplasty for patients with improvement with Botox, and implantation of gastric neurostimulation.

To refer patients to California Pacific's Motility Services, or for further information on gastric electrical stimulation, contact our Specialty Referral Line at 1-888-637-2762.

Gatekeeper System Study

The Gatekeeper System is designed to create a barrier that allows food and liquids to pass normally into the stomach, while restricting acid and other stomach contents from refluxing back up into the esophagus. With this treatment, which is delivered endoscopically, several prostheses the size of pencil lead cartridges are inserted near the lower esophageal sphincter. The prostheses are made of an inert hydrogel similar to the substance used in contact lenses. The prostheses absorb moisture from surrounding tissue and expand to six-fold their original size, creating a mechanical barrier to reflux.

“What is unique about this procedure is its reversibility,” says Kenneth Binmoeller, M.D., director of California Pacific’s Interventional Endoscopy Service. “The implants can be removed in literally seconds with a simple endoscopic procedure,” he adds.

As one of 10 centers in the United States studying this therapy, California Pacific is enrolling patients through early summer. In all, about 200 patients will be studied nationwide. For trial enrollment, patients must be at least 18 years old with documented symptoms of GERD (heartburn and substernal pain). Additionally, the patient must be taking a proton pump inhibitor (PPI) such as Nexium®, Aciphex® or Protonix® and have some symptom relief while taking the medication. Exclusion factors include severe esophagitis,

extensive Barrett’s Esophagus, esophageal or gastric varices, and morbid obesity.

GERD Cases and Side Effects on the Rise

GERD is caused by a dysfunctioning lower esophageal sphincter (LES). Normally, the LES prevents gastric contents from refluxing into the esophagus and irritating the esophageal lining. When the LES relaxes too frequently or its resting pressure drops, GERD occurs. If untreated, complications of GERD can result, including stricture, ulcers and bleeding. Importantly, chronic GERD can lead to precancerous change known as Barrett’s esophagus and cancer itself. Barrett’s arises from an abnormal repair following mucosal injury induced by gastroduodenal refluxate. The risk of Barrett’s in patients with GERD may be 40 to 125 times that of the general population. In the past 20 years, adenocarcinoma of the esophagus has increased six-fold, the fastest growing cancer of any kind. This dramatic rise is mainly attributed to an increasing incidence of GERD.

Guidelines for Heartburn Evaluation

A step-wise approach to treatment of GERD is recommended, starting with pharmacologic therapy. Endoscopic treatment should be considered if pharmacologic therapy is either not tolerated or inconvenient. The following screening guidelines have emerged for the evaluation of heartburn:

- Patients with long-standing GERD



Gatekeeper hydrogel prosthesis in the unexpanded (left) and expanded (right) states.

symptoms should have upper endoscopy to detect Barrett’s

- White males with chronic GERD symptoms, particularly those over age 50, are at high risk for Barrett’s and should undergo evaluation with upper endoscopy
- Patients of any age with heartburn and dysphagia, or those who have not responded to medication, should undergo upper endoscopy

Treatment of the underlying cause of GERD may also be preferred. Surgery is indicated for patients with a large hiatal hernia or inadequate response to endoscopic treatment.

To refer patients to California Pacific’s Interventional Endoscopy Service, contact our Specialty Referral Line at 1-888-637-2762. For further information on the Gatekeeper Study, contact Danielle Hauptman, RN, clinical research coordinator, at 415-600-1773 or hauptmd@sutterhealth.org.



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