Division of Gastroenterology, Hepatology, and Nutrition

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Nutrition Options in Short-Bowel Syndrome

By David G. Binion, MD, and Zachary Zator, MD

Intestinal transplantation is an option for select patients with short-bowel syndrome-associated intestinal failure (SBS-IF) who fail or do not tolerate nutritional rehabilitation. There are a range of factors to consider in the nutritional management of patients before and after intestinal transplantation.

SBS-IF can be defined as the inability to maintain proper nutritional balance — including of proteins, electrolytes, macronutrients, micronutrients, and fluids — while adhering to a conventional diet in the face of an anatomically or functionally limited gut surface. The ideal management of patients with SBS-IF involves a multidisciplinary team of gastroenterologists, nurses, dietitians, pharmacists, and surgeons. Pharmacotherapeutic agents aimed at minimizing fluid losses have been routinely employed to support these patients. For instance, antidiarrheal agents, such as loperamide or diphenoxylate, are used alongside proton pump inhibitors. Somatostatin analogs, like octreotide, inhibit gastrointestinal secretions from the stomach, pancreas, and intestines and have been proven beneficial in the past. However, their role can be limited, as somatostatin can actually inhibit enteral protein synthesis. In recent years, attention has turned beyond mere supportive care to potentially therapeutic pharmacologic agents, such as teduglutide, a human recombinant GLP-2 analog, which was approved in 2012.

Glucagon-like peptide-2 (GLP-2) is secreted in response to luminal nutrients reaching the distal ileum and colon, and promotes the growth of intestinal mucosa by increasing mesenteric blood flow, decreasing gastric acid secretion, and enhancing crypt cell growth

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Disclosures: Dr. Binion reports grants and research support from Janssen Biotech, Merck, and UCB Pharma, and he also serves as a consultant for Janssen Biotech, AbbVie, UCB Pharma, and Synthetic Biologics. All other contributing authors and editors of this publication report no relationships with proprietary entities producing health care goods and services.

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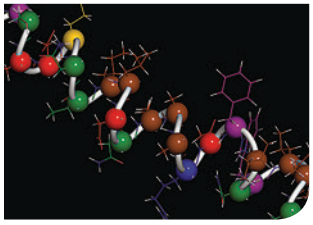
Nutrition Options in Short-Bowel Syndrome *(Continued from Page 1)*

while inhibiting apoptosis. However, the endogenous form of GLP-2 is rapidly degraded in vivo. As a recombinant analog of GLP-2, teduglutide has a significantly longer half-life and acts by binding to GLP-2 receptors and potentiating its effects. In phase III randomized, placebo-controlled trials, the volume of parenteral support that patients required was significantly reduced in those patients receiving teduglutide.[1,2] The medication is fairly well tolerated, with abdominal pain (30%), minor injection-site reactions (22%), nausea (18%), and headaches (16%) being the most commonly reported adverse effects. Given the nature of the drug, theoretic concerns exist related to tumor promotion, and colonoscopy is recommended six months before and one year after drug initiation.



When medical management of SBS-IF fails, intestinal transplantation is pursued in select patients. The optimal strategy to manage nutritional needs in these complex postoperative patients is not entirely known. Moreover, requirements vary depending on the length of time since transplantation. Right after transplant, patients generally need higher caloric intake to maintain a healthy nutritional state. Yet at three months after transplantation, the enteral graft generally absorbs carbohydrates and other forms of energy quite well. In one pediatric study, a ratio of energy intake to resting energy expenditure of 1.34 ± 0.18 was needed for patients on full parenteral nutrition (PN), compared with a ratio of 2.15 ± 0.27 for full enteral intake.[3] Long-term data from a different study suggests that these escalated enteral requirements may decrease over time. Ensuring that patients meet these needs while transitioning from parenteral to enteral nutrition is critical to nutritional homeostasis. From a practical perspective, it is important to recognize that the enteral energy needed to maintain adequate nutrition is highest early after transplant, but likely returns closer to the population norms over time. These early nutritional demands can be met through increased caloric intake.

Outside of caloric requirements in the posttransplant population, attention must be paid to maintaining adequate hydration. Nearly all patients who undergo intestinal transplantation are managed with an ileostomy for at least the initial period after transplant. The ileostomy facilitates endoscopic biopsies to monitor for rejection but also bypasses the absorptive surface of the colon. In general, ostomy output greater than 40 mL/kg/d is considered increased. In this scenario, underlying infection (viral, bacterial) should be investigated, accompanied by supportive care with fluid supplementation.

Following intestinal transplantation, patients are at risk for specific micronutrient deficiencies, and careful monitoring and treatment are essential to avoid complications. The most common deficiencies seen in one pediatric study after transition to enteral nutrition were iron (94.7%), magnesium (90.5%), zinc (50%), vitamin D (66.7%), and vitamin A (40%).[4] Another study found that almost all patients (96%) were deficient in the active form of vitamin B_6 within 30 days of transplantation.[5] As a result, proactive supplementation with both a multivitamin and micronutrient-specific formulations is considered necessary in the posttransplant population.

Proper nutritional management of patients before and after intestinal transplantation involves a directed, multidisciplinary approach aimed at defining, monitoring, and eliminating deficiencies in individual patients. With the help of supportive care techniques and novel pharmacologic agents like teduglutide, patients with short bowel syndrome-associated intestinal failure can be managed successfully. If intestinal transplantation is required, careful attention must be paid to not only caloric requirements, but also to hydration status and micronutrient and macronutrient homeostasis.

Dr. Binion is a professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition. He serves as a co-director and translational research leader for the IBD Center and directs the Division's Nutrition Support Program.

Dr. Zator is a year III gastroenterology fellow with the Division of Gastroenterology, Hepatology, and Nutrition, where he also serves as the chief GI fellow.

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Gastric Carcinoids with Duodenal Ulcers: A Hint for Diagnosis of Multiple Endocrine Neoplasia Type I (MEN1)

By Cynthia Cherfane, MD

CASE PRESENTATION

A 65-year-old man with a history of coronary artery disease was admitted to the hospital for non-ST segment elevation myocardial infarction (NSTEMI). He underwent percutaneous coronary intervention and was started on aspirin and clopidogrel. His course was complicated by an intracranial hemorrhage and coffee ground emesis.

His past medical history included hyperparathyroidism and islet cell tumor co-secreting gastrinoma/glucagonoma status post distal pancreatectomy in 1994. Family history was significant for heart failure in his father and prolactinoma in his mother. He does not smoke or drink alcohol.

Upper endoscopic examination revealed LA grade D esophagitis and multiple small polyps (5 to 10 mm) in the gastric fundus and body. Multiple superficial ulcers in the second portion of the duodenum were also evident. Gastric polyp biopsies were positive for well-differentiated, low-grade carcinoid involving the oxyntic and muscularis mucosa. Gastrin and chromogranin levels were measured after stopping proton pump inhibitors (PPI) and were shown to be elevated.

Based on the history of pancreatic neuroendocrine tumor, hyperparathyroidism, and family history of pituitary adenoma, this patient most likely had multiple endocrine neoplasia type 1 (MEN1) syndrome. MEN1 is an autosomal dominant disorder characterized by three primary tumor sites: the pituitary, parathyroid, and pancreas. Other tumors, such as gastric carcinoid tumors type II, adrenal adenomas, and lipomas, have been described in these patients.

There are four types of gastric carcinoids. Gastric carcinoid type II constitutes 5% to 10% of gastric carcinoids, and is the type associated with MEN1 and Zollinger-Ellison syndrome (ZES).

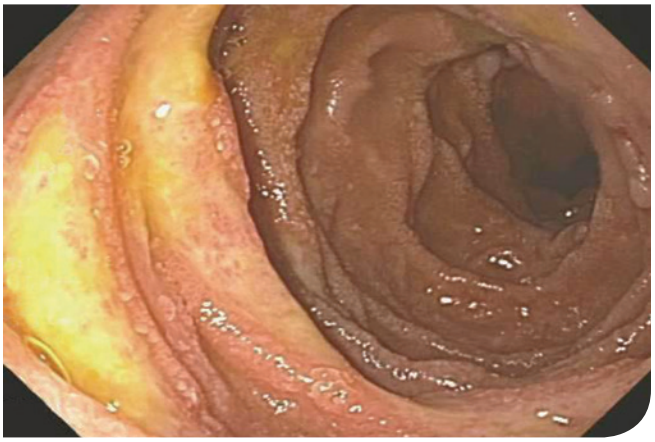


Figure 1. Large ulcers in the second portion of the duodenum in the setting of MEN1 and Zollinger-Ellison syndrome.

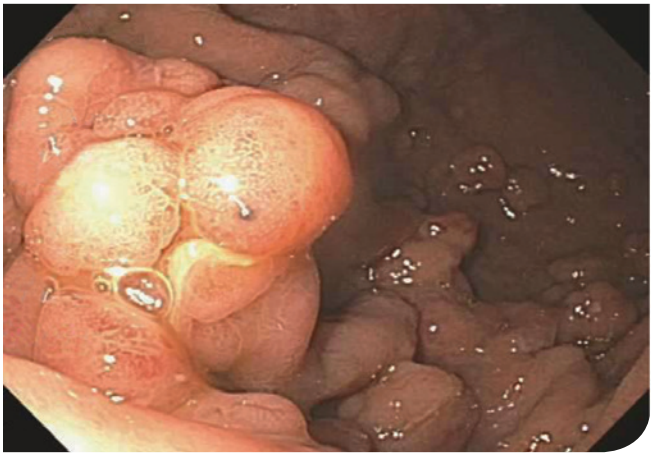


Figure 2. Gastric polyps with biopsies positive for carcinoid tumor.

These tumors are usually small (< 1 cm) and multifocal. They are well differentiated with low risk of metastasis (< 10%) and have a good prognosis. A low gastric pH differentiates type II from type I and is thought to result from the concomitant presence of a gastrinoma. MEN1 patients have a 20- to 30-fold higher risk of developing a gastric carcinoid tumor compared to patients with sporadic ZES. Patients who are not known to have MEN1

Continued on Page 7

Living-Donor Liver Transplant (LDLT): Time to Shift the Paradigm

By Abhinav Humar, MD, and Swaytha Ganesh, MD

Liver transplantation has been well established as a therapeutic option for patients with various end-stage liver diseases (ESLD). The first successful liver transplant was performed by Thomas Starzl, MD, in 1967, back when deceased donors were the primary source of the liver for transplantation. Due to significant shortages of deceased donor organs and the long wait for liver transplantation, attempts have been made to expand the donor pool, including the use of livers from marginal donors, split livers from deceased donors, and transplants from living donors.

THE PROBLEM

Living-donor liver transplant (LDLT) provides a lifesaving option for patients with end-stage liver disease. A portion of a healthy liver from a family member, friend, or altruistic donor is transplanted into the recipient. Due to the liver's unique ability to regenerate, LDLT offers a viable option for both the recipient and the donor. The United Network for Organ Sharing (UNOS) has allocated deceased donor livers based on the Model for End-Stage Liver Disease (MELD) score since February 2002. The MELD allocation is now based on MELD-Na as of January 2016. The donor organs are offered to patients with the highest risk of death, based on the MELD. Prior to the MELD era, liver allocation was based on the Child-Turcotte-Pugh score.

MELD-Na is heralded for its objectivity and its success in reducing wait-list mortality, but some aspects concerning medical urgency for liver transplants are not accurately represented by the MELD. Survival cannot be predicted precisely in 15% to 20% of cases, and mortality risk among the 24.4% of patients with ascites is underestimated.

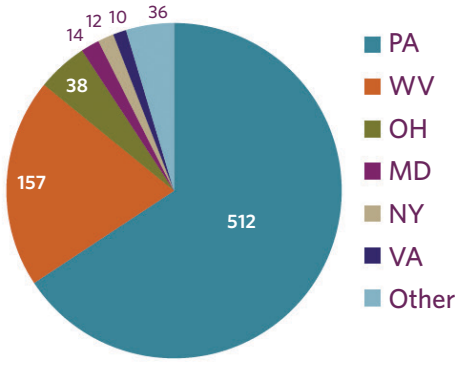
More than 16,000 people are currently on a wait list for a liver transplant, with only an estimated 5,000 deceased donor transplants and 250 living donor transplants done per year (i.e., less than 40% of patients on the wait list are transplanted per year). One out of every five patients either dies or is removed from the list, and the overall wait-list mortality in the United States is approximately 17%, with a range of 10% to 28%. The number of deceased donor transplants has not increased incrementally from 1991 to 2016, but the wait list continues to grow each year. LDLT offers a solution to organ shortages while also serving as a lifesaving option for patients.

Due to patients' long wait-list periods (up to two years) and changes in the liver allocation policies, as well as regional disparities, LDLT is a crucial, lifesaving option. The mean MELD score is now much higher (> 30) to obtain a transplant, especially in the greater Pittsburgh region, where UPMC now transplants patients with very high MELD scores. About 25% of wait-list patients die while on the list without an opportunity to receive a transplant.

PROGRAM VOLUMES

- **Living-Donor Liver Transplant (LDLT)**
  - — 96 total LDLTs performed at UPMC (adult and pediatric) since 2010*, making up:
    - 42% of Region 2 volumes
    - 58% of state volumes
    - 7% of national volumes
  - — UPMC is the only center performing LDLT in western Pennsylvania

Liver TX Referrals By State, 1/2013–12/2014



** Source: Organ Procurement and Transplantation Network, Accessed 12/22/14*

Table 1: Improved Outcomes With LDLT

- Surgery can be provided at a lower MELD score, leading to better surgical outcomes
- Patients experience a shorter length of stay in the hospital, and recovery time is reduced
- Postoperative complications, such as renal failure, are less likely
- Cold ischemic time is lower
- Immunological advantages are evident
- Surgery can be scheduled at a convenient time for both patients and the surgery team
- Huge opportunity for family, friends, and the community to make a difference and save lives

INDICATIONS FOR LDLT

Any patient on the wait list with high risk of decompensation and a MELD-Na of less than or equal to 30 is a candidate for LDLT. Patients with hepatocellular carcinoma (HCC) within criteria qualify too, and sometimes qualify even with extended criteria. Feasibility of LDLT in HCC is not restricted by the national allocation system and depends on institutional policies. Operative risks for donors and survival benefits for recipients need to be considered carefully, especially for patients with worrisome prognostic signs who are low on the waiting list, as well as for patients with metabolic and rare diseases who do not fall within UNOS criteria. LDLT is also offered to international patients at UPMC.

BENEFITS OF LDLT

LDLT is an elective, nonemergent surgery that eliminates wait times. Studies show it can offer better outcomes (Table 1). The LDLT patient goes to surgery before further liver disease complications take hold (e.g., bleeding, infections, hospitalizations, etc.).

The new liver is more likely to survive when it comes from a living donor. LDLT survival is 85% to 90% at one year after the transplant. Ten-year survival is 70%, compared to 64% for patients who received a deceased donor transplant.

Of course, one LDLT translates to one less person on the wait list for a deceased donor liver. Living donation reduces the wait time and increases transplant accessibility for patients who might otherwise not receive a liver.

WHY UPMC

Within the tenure of Dr. Abhinav Humar's leadership, the UPMC Liver Transplant Program leads the nation in overall liver transplants performed from both deceased and living donors. Of the total liver transplants performed annually, approximately 25 are complex living donor transplants. An extremely skilled team of transplant surgeons, hepatologists, liver transplant nurse coordinators, and psychiatrists collaborate closely to guide each patient from pretransplant assessments through postdischarge follow-ups, ensuring the best possible outcomes.

At UPMC, we also value the knowledge and expertise of a patient's referring physician, who is recognized as a partner throughout the transplant process.

UPMC's Liver Transplant Program has distinguished itself among other centers due to its commitment to accept challenging and complex cases. UPMC's history, experience, research acumen, and clinical resources provide truly comprehensive care for patients with end-stage liver disease.

CONTACT US

Visit UPMCPhysicianResources.com/GI to see Dr. Humar and Dr. Ganesh, as well as transplant surgeon Christopher Hughes, MD, discuss LDLT from early patient identification and referrals to full evaluation for a successful transplant.

For more information or to refer a patient, call **1-844-UPMC-LIVER** or visit **UPMC.com/LivingDonorLiver.**

Dr. Humar is a professor of surgery and serves as the clinical director for the Thomas E. Starzl Transplant Institute and as chief for the Division of Transplantation within the UPMC Department of Surgery.

Dr. Ganesh is an assistant professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition and serves as the medical director of the Living Donor Liver Program for the Thomas E. Starzl Transplant Institute.

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HONORS AND AWARDS

Miguel Regueiro, MD, has been chosen to chair Advances in Inflammatory Bowel Disease, the national IBD subspecialty annual meeting in Orlando, Florida. Advances in IBD will occur from November 9–11, 2017. Dr. Regueiro will be joined by fellow co-chairs Richard MacDermott, MD, from the Albany Medical Center, and Stephen Hanauer, MD, from the Northwestern Feinberg School of Medicine. Dr. Regueiro is a professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition, where he co-directs and provides clinical leadership for the IBD Center and Total Care-IBD, UPMC's IBD subspecialty medical home.

Eva Szigethy, MD, PhD, was awarded a $100,000 Sherman Prize for her work to develop psychosocial care models for IBD patients. Dr. Szigethy was honored with this recognition during the Bruce & Cindy Sherman Foundation's inaugural prize year. The Sherman Prize in Crohn's and Colitis rewards the delivery of excellent care and seeks to honor efforts which are not only life-changing for patients but duplicative among the IBD physician and medical professional community. Dr. Szigethy is a professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition, where she also serves as the founder and director of the Visceral Inflammation and Pain (VIP) Center and co-directs Total Care-IBD, UPMC's medical home, with Dr. Regueiro.

What Is This? *(Continued from Page 8)*

The esophageal findings described as whitish plaques were brushed for cytology and biopsied for histology. Cytology demonstrated reactive squamous epithelial cells and herpes viral cytopathic effect. Histology demonstrated herpes esophagitis confirmed by immunostain.

Herpes simplex virus (HSV) esophagitis usually is diagnosed in immunocompromised patients, particularly following bone marrow or solid organ transplantation. Pathogenesis involves reactivation of HSV with spread of the virus to the esophageal mucosa by way of the vagus nerve, or by direct extension of oropharyngeal infection into the esophagus. Lesions usually affect the squamous mucosa of the distal esophagus. Vesicles develop initially and then coalesce to form ulcers that are usually present with normal-appearing intervening mucosa. Exudates, plaques, or diffuse erosive esophagitis can also be present. Biopsies or brushing should be taken from the edge of an ulcer where viral cytopathic effects are most likely to be present. Histologic findings include multinucleated giant cells containing intranuclear clearing and eosinophilic inclusions. Immunostain for HSV glycoproteins and viral culture are also helpful in diagnosis. Acyclovir is the most common medication used in treatment. Dosage in immunocompromised patients is usually 400 mg orally, five times per day for two to three weeks. Alternatives include famciclovir or valacyclovir. Intravenous acyclovir is used in patients with severe odynophagia or dysphagia. Immunocompetent patients can have spontaneous resolution within one to two weeks, but a short course of acyclovir can decrease symptom duration.

This case demonstrates an uncommon presentation of HSV esophagitis in which the patient was immunocompetent and asymptomatic.

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Gastric Carcinoids with Duodenal Ulcers *(Continued from Page 3)*

syndrome, and have a gastric carcinoid associated with ZES, should undergo genetic testing for MEN1.

Once diagnosis of the type and grade of the gastric carcinoid is established, the stage of the tumor should be determined. This will necessitate an endoscopic ultrasound of the gastric lesion and abdominal imaging (CT or MRI) +/- an octreotide scan. The goal is to determine the local extent and presence of metastases and, if possible, to localize the gastrin-secreting tumor, which is usually located in the pancreas or duodenal wall. Type II gastric carcinoid tumors should be resected. This can be done endoscopically if the lesion is localized or surgically if metastases are present. Conversely, there is no good evidence that the resection of gastrinomas, which are usually small and multifocal, improves mortality or decreases the risk of metastases. Proton pump inhibitors should be used for all patients with ZES.

CONCLUSION

Our patient will be scheduled for an endoscopic ultrasound and abdominal imaging for staging and localization of the gastrinoma. Depending on the stage, he will undergo either endoscopic or surgical resection of the gastric carcinoids, with surveillance every 6 to 12 months. He should be continued on long-term PPI for ZES. As part of surveillance for his MEN1, he will also require a brain MRI and repeat calcium, prolactin, and PTH.

Dr. Cherfane is a year III gastroenterology fellow with the Division of Gastroenterology, Hepatology, and Nutrition

Pittsburgh Gut Club

The **Pittsburgh Gut Club** is a gastroenterology education and networking series designed to bring novel and relevant subspecialty advancements to the greater Pittsburgh region. All gastroenterologists, physicians, and allied health professionals are encouraged to attend. Programs are from 6 to 8:15 p.m. at the University Club, 123 University Place, Pittsburgh, Pennsylvania.

Learning Objectives:

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- Review the latest procedural and diagnostic advancements for gastroenterology practice
- Identify current treatments available for GI diseases and discuss future advancements

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Comparative Effectiveness of Biologic Therapy in IBD: Which One, When?

Hans Herfarth, MD, PhD
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University of North Carolina
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April 20, 2017

Advances in Irritable Bowel Syndrome

Michael Camilleri, MD
Professor of Medicine, Pharmacology & Physiology
Department of Gastroenterology & Hepatology
Mayo Clinic, Rochester, Minnesota

Contact Information:

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What Is This?

Mohannad Dugum, MD
Gastroenterology Fellow, Year II
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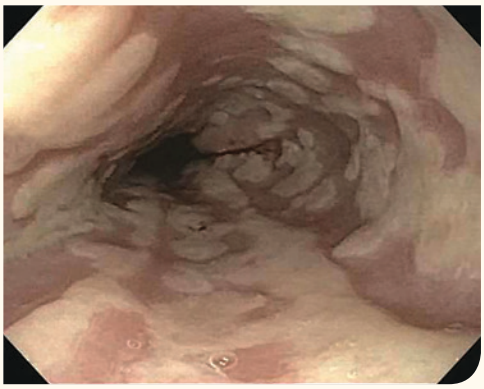
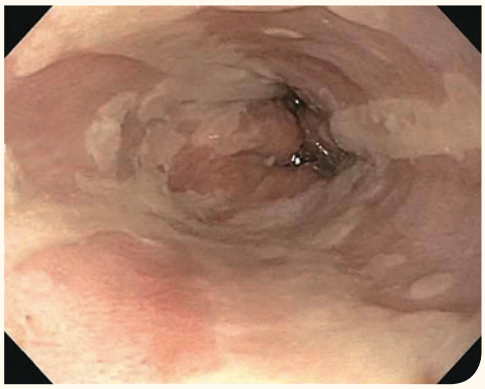
CASE PRESENTATION

A 66-year-old male with a history of diabetes and squamous cell lung cancer was admitted for management of a ruptured abdominal aortic aneurysm. He had an inpatient episode of coffee ground emesis. Upper endoscopy revealed a duodenal ulcer with visible vessel, which was treated with thermal therapy. He was also found to have the following findings in the esophagus. He denied dysphagia, odynophagia, heartburn, or chest pain. What is this?

Compare your answer to Dr. Dugum's on Page 6.





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