One year, two key numbers

For Cleveland Clinic’s Center for Gut Rehabilitation and Transplantation, 2013 was in large part a year of two numbers:

- 9, the number of visceral transplants performed — Cleveland Clinic's second-highest single-year volume to date, including its first pediatric visceral transplant and first visceral transplant in a patient with HIV
- 98, the number of intestinal surgical rehabilitation procedures performed, representing many dozens of patients in whom visceral transplantation (and lifelong immunosuppression) was avoided

These two numbers exemplify the comprehensive approach the Center for Gut Rehabilitation and Transplantation brings to bear for patients with intestinal failure. That approach yielded a number of other notable outcomes and statistics in 2013, as detailed in the graphs that follow and the points below:

- 87.5 percent one-year patient survival among intestinal transplant patients, which compares favorably with the national average of 80.5 percent (per data from the Scientific Registry of Transplant Recipients as of April 2014)
- 211 patients referred to the center in 2013, a fourfold increase over the 2011 level
- 56 percent success rate in achieving nutritional autonomy using autologous gut among patients undergoing surgical intestinal rehabilitation

9 visceral transplants in 8 patients in 2013, including:
- 7 intestine alone
- 1 intestine-liver-pancreas-duodenum
- 1 full multivisceral
Transplant: One piece of a comprehensive approach

Cleveland Clinic is among the world’s few centers that offer both intestinal and multivisceral transplantation, and its volume of nine such transplants in 2013 was one of the highest in the U.S. The visceral transplant team draws on the expertise of multiple accomplished abdominal transplant surgeons, a cadre of subspecialized gastroenterologists and a team of transplant coordinators, among others.

But transplantation is just one component of the Center for Gut Rehabilitation and Transplantation, which represents one of the world’s largest and most comprehensive programs for intestinal rehabilitation and restoration of gastrointestinal autonomy.

The multidisciplinary center’s range of options for adult and pediatric patients with intestinal failure is unsurpassed and includes:

- **Home parenteral nutrition** (HPN) support from Cleveland Clinic’s Center for Human Nutrition, which cares for the largest HPN cohort followed by a single U.S. center and is recognized as a program of excellence by the American Society for Parenteral and Enteral Nutrition.

- **Expert medical management** by the Center for Human Nutrition, including intensive, personalized diet counseling with use of oral rehydration solutions, enteral feeding, and (if necessary) medications or growth factors, including the new glucagon-like peptide 2 analog teduglutide (Gattex®). Specialized pharmacists and dietitians work closely with supervising gastroenterologists to reduce or potentially eliminate the need for HPN and improve patients’ quality of life.

87.5% one-year patient survival, better than national average of 80.5%

*The first of the 2013 transplants was performed in July 2013. Last follow-up was April 25, 2014.*
“Visceral transplantation” generally refers to transplant procedures that include the intestine. There are four main types:

1. Intestine alone
2. Liver, intestine and pancreas
3. Full multivisceral (stomach, duodenum, pancreas, intestine and liver)
4. Modified multivisceral (stomach, duodenum, pancreas and intestine)

The number of patients who undergo visceral transplant is considerably lower than for other solid organ transplants, and far fewer centers perform visceral transplants. Transplants involving the intestine pose a greater immunologic challenge than do other transplant types, but outcomes have improved substantially with the introduction of new immunosuppressive protocols in recent years.

Absolute indications for intestinal transplant alone or with other organs include failure of home parenteral nutrition (HPN) with development of related complications. Current Centers for Medicare & Medicaid Services criteria define HPN failure as:

- HPN-associated liver injury
- Central venous catheter-related thrombosis of two or more central veins
- A single episode of line-related fungal infection
- Frequent episodes of central line bacterial infection
- Frequent episodes of severe dehydration despite IV fluid replacement in conjunction with HPN
- Ultra-short gut syndrome

DEFINING TERMS IN VISCERAL TRANSPLANT

Intestine alone  Liver, intestine and pancreas
Full multivisceral  Modified multivisceral
Innovative surgical procedures for intestinal rehabilitation, to enhance the absorptive function of the residual native intestine in selected patients, many of whom are able to discontinue HPN. The most commonly used procedures are:

- Autologous intestinal reconstruction (67 percent of Cleveland Clinic’s intestinal rehabilitation surgeries in 2013). These procedures include repair of multiple enterocutaneous fistulae and restoration of gastrointestinal continuity with take-down of intestinal and colonic stoma.

- Bowel-lengthening procedures such as the Bianchi procedure and serial transverse enteroplasty procedure (STEP; see images) (17 percent of 2013 surgeries).

- Foregut gastric reconstruction (16 percent of 2013 surgeries). Gastric reconstruction with restoration of gut continuity is increasingly required for patients who undergo gastric bypass surgery at other centers and develop intestinal failure after a catastrophic abdominal event; few if any other centers are able to offer this procedure.

Inventive reconstructive operations for patients with highly complex abdominal pathology (e.g., “hostile abdomen”) that most centers will not take on. These include patients with abdominal cocoon syndrome, extensive abdominal adhesions, multiple enteric fistulae and extensive thrombosis of the portal venous system.

A nuanced, customized approach to challenging cases

The above options are considered for all appropriate patients before visceral transplant, to avoid the unique risks and need for lifelong immunosuppression that transplant confers.

The result is a creative approach to challenging patients that goes far beyond a simple “transplant/no transplant” dichotomy to find the best customized solution for a given patient. The approach includes a novel Intestinal Stroke Center for timely multidisciplinary management of patients with vascular insufficiency of the intestine (see sidebar, opposite page).
NOVEL INTESTINAL STROKE CENTER PROMOTES SWIFT RESCUE FOR INTESTINAL ISCHEMIA

Patients with acute intestinal ischemia need optimal management immediately. To provide such management as swiftly as possible, the Center for Gut Rehabilitation and Transplantation recently established an unprecedented Intestinal Stroke Center that employs a multidisciplinary team approach. The aim is to restore blood flow to the intestine and other abdominal organs through innovative combinations of medical management with radiologic and/or surgical intervention. Based on cerebrovascular stroke protocols, the Intestinal Stroke Center ensures 24/7 availability of expert clinicians — including acute care surgeons, intensivists, Center for Gut Rehabilitation and Transplantation surgeons and gastroenterologists, diagnostic and interventional radiologists, hematologists, and infectious disease specialists — and uses a standardized management algorithm to:

- Offer timely intervention to reduce propagation of mesenteric thrombosis and minimize the time of ischemia
- Increase chances of intestinal viability, reduce permanent ischemia to the bowel and salvage as much bowel as possible

In its first 15 months of operation, spanning 2012 and 2013, the Intestinal Stroke Center managed 127 patients across 131 encounters, with most patients being rescued with salvage of the abdominal organs that were viable on referral. The center’s management algorithm ultimately leads to visceral transplant for patients who have permanently lost their gut.

Research and innovation: Building on a rich legacy

The Center for Gut Rehabilitation and Transplantation’s tradition of innovation got a major boost with the arrival of Kareem Abu-Elmagd, MD, PhD, as its new director in August 2012.

Dr. Abu-Elmagd is the world’s most experienced surgeon in intestinal transplantation, having been involved in approximately 20 percent of all such procedures worldwide. His many significant contributions to intestinal and multivisceral transplantation, immunosuppression, transplant immunology and allograft tolerance include the following:

- First demonstration in humans of the immunoprotective effect of the engrafted liver on other simultaneously transplanted visceral organs
- Introduction of a novel tolerogenic immunosuppressive protocol in humans, achieving unprecedented outcomes that include successful complete discontinuation of immunosuppression in a few immune-privileged visceral transplant recipients
- Introduction of the concept of gut rehabilitation with medical and surgical modalities, including innovative autologous reconstructive procedures for patients with complex abdominal pathology and intestinal failure

Dr. Abu-Elmagd is now working with his Center for Gut Rehabilitation and Transplantation colleagues to build on those advances through a number of research and clinical initiatives, including:

- Efforts to develop novel anti-donor-specific antibody strategies for use in liver-free visceral allografts that lack hepatic immunoprotection. This work includes refining a preconditioning protocol involving the proteasome inhibitor bortezomib that Dr. Abu-Elmagd recently introduced for patients with detectable donor-specific antibodies. The protocol has shown encouraging results and is now being implemented by other centers for visceral transplantation.
- Bench research focusing on the repertoire of lymphocytes following visceral transplant to identify a noninvasive clinical biomarker for intestinal allograft rejection to enable earlier detection and treatment of rejection.

The alternatives to visceral transplant are frequently successful: Full nutritional autonomy (freedom from HPN) was achieved in 56 percent of patients (N = 74, who collectively underwent 98 procedures) undergoing surgical rehabilitation at Cleveland Clinic in 2013. The remaining patients underwent continual gut rehabilitation with the new medication teduglutide or proceeded to intestinal transplant.

Even when visceral transplant is unavoidable, the full multidisciplinary resources of the Center for Gut Rehabilitation and Transplantation are deployed for judicious monitoring of organ function and evaluation for infection, malignancy and other systemic disorders while patients await organ availability and during the crucial postoperative and recovery periods.

Application of visceral transplantation to new and nontraditional indications and patient populations (see sidebar at left).

Innovative approaches for the management of patients with rare gastrointestinal disorders.

Leadership in patient advocacy

Dr. Abu-Elmagd has been in the vanguard of patient advocacy in intestinal failure since he played a lead role in convincing the Centers for Medicare & Medicaid Services (CMS) in 1999 to provide reimbursement for intestinal and multivisceral transplantation as the standard of care for irreversible intestinal failure.

Currently Dr. Abu-Elmagd and Cleveland Clinic are helping lead the call for two important initiatives in this area:

- Modification of United Network for Organ Sharing regulations to permit national sharing of deceased donor intestinal allografts according to favorable HLA and virtual cross-match results
- Loosening of CMS controls on current indications for intestinal transplant

Prioritizing pediatric transplant

Cleveland Clinic performed its first visceral transplant in a pediatric patient in 2013 (involving intestine, duodenum, liver and pancreas; see patient sidebar) and is poised to perform increasing numbers to address unmet needs in this population.

Understanding of those needs has been significantly shaped by Dr. Abu-Elmagd's pioneering research on the quality-of-life aspects of visceral transplantation in children and adults (Ann Surg. 2012;256(3):494-508), which suggests that early consideration should be given to gut rehabilitation, including transplantation, to potentially reduce the risk of autism, developmental delay and behavioral disorders in pediatric patients with intestinal failure.

Appropriate candidates for pediatric visceral transplant include children with short bowel syndrome, congenital anomalies, necrotizing enterocolitis, intestinal atresia, midgut volvulus, gastrochisis and motility disorders.

Cleveland Clinic’s pediatric intestinal and multivisceral transplant services are highly integrated with Cleveland Clinic Children’s well-established Pediatric Intestinal Rehabilitation Program and Pediatric Nutrition Program to ensure a comprehensive overall treatment approach and expert pre- and post-transplant care.
When 3½-year-old Khaled Mahamid arrived at Cleveland Clinic in August 2012, he had already long defied medical expectations.

Born in the Middle East with Martinez-Frias syndrome, Khaled was the first child known to have survived so long with the rare inherited disorder marked by a host of life-threatening complications. In Khaled’s case, these included neonatal diabetes, enterocyte failure and iron overload with end-stage cholestatic liver disease. Since birth, he had required total parenteral nutrition (TPN) and multiple daily insulin doses.

Khaled’s doctors suggested that his parents explore a transplant abroad. They eventually found Kareem Abu-Elmagd, MD, PhD, Director of Cleveland Clinic’s Center for Gut Rehabilitation and Transplantation. He proposed a complex visceral transplant to provide Khaled with a new intestine, duodenum, liver and pancreas.

“The fact that Khaled had survived longer than any other patient with Martinez-Frias syndrome prompted us to try to give him a second chance through transplantation,” explains Dr. Abu-Elmagd.

After more than a year of intricate inpatient care at Cleveland Clinic Children’s to manage Khaled’s TPN, fluid balance and diabetes, suitable donor organs became available. In September 2013, Khaled, then 4½, underwent the 15-hour, five-surgeon transplant procedure. It was a success, with all three organs and the duodenum grafting well.

Khaled was discharged less than two months later on an unrestricted oral diet and with his diabetes cured. At seven months after transplant, he was faring well, with no need for insulin and enjoying his unrestricted diet to full extent. “His favorite foods include mussels, octopus and lobster!” his mother recounts.

Dr. Abu-Elmagd says he is gratified “to be able to show humanity this outcome” in a disease with such a traditionally dismal prognosis, but he is even more pleased to help give Khaled a second chance at life. “I am confident he won’t have recurrent disease with the new organs,” he says.

Khaled is back home in the Middle East, but Dr. Abu-Elmagd and his team will continue to monitor Khaled to study what happens when someone with Martinez-Frias syndrome ages and grows — something that had never been possible before.