# Visceral Transplantation: Current Trends and Long-Term Outcome

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**Abstract**

The successful development of visceral transplantation is one of the milestones in the recent history of human organ transplantation. All types of gastrointestinal transplantation have evolved to be the standard of care for patients with gut failure and complex abdominal pathology. The outcome has markedly improved over the last three decades due to technical innovation, novel immunosuppression, and better postoperative care. Recent data documented significant improvement in the long-term therapeutic indices of all types of visceral transplantation close to that achieved with thoracic and other solid abdominal organs.

**Keywords**

Intestinal transplantation · Parenteral nutrition · Visceral transplantation · Intestinal

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A. P. Shah et al. (eds.), *Contemporary Pancreas and Small Bowel Transplantation*, Organ and Tissue Transplantation, https://doi.org/10.1007/978-3-319-05257-1_25

failure · Portomesenteric venous thrombosis · Transplant evaluation · Graft survival · Quality of life

## Introduction

Prior to the introduction of parenteral nutrition (PN) in 1968, the condition of gastrointestinal (GI) failure was fatal. The use of PN significantly improved survival in patients with gut failure, although was soon linked with life-threatening complications such as catheter related sepsis, PN-induced liver disease, and line-associated thrombus. Unfortunately, the intestinal tract was considered a forbidden organ for clinical transplantation due to the associated massive lymphoid tissue, high antigenicity, and microbial colonization (Abu-Elmagd et al. 2009a; Grant et al. 2015). The practical application of visceral transplantation only became feasible after the 1989 advent of FK-506 (Prograf, tacrolimus) (Starzl 1989). New advances in surgical techniques, immunosuppressive strategies, and postoperative management allowed for the continual evolution of the procedure (Grant et al. 2005, Abu-Elmagd et al. 2009b).

In 2000, the US Centers for Medicare and Medicaid Services (CMS) qualified intestinal and multivisceral transplantation as the standard of care for patients with irreversible gut failure who no longer can be maintained on PN (Abu-Elmagd et al. 2002) Intestinal failure (IF) is defined as the inability to maintain nutrition or adequate fluid and electrolyte balance without intravenous (IV) support, due to severe impairment of the primary enteric digestive, absorptive, neuroendocrine, and/or motor functions (Abu-Elmagd et al. 2001). Irreversible IF is declared only after comprehensive medical and surgical rehabilitative measures that may control adverse symptoms, enhance gut function, augment adaptation, and/or treat the primary disease fail to allow weaning from PN. Resection of over 80% of the small bowel along with most of the colon and the ileocecal valve is usually associated with poor adaptation and the development of permanent IF.

## Nomenclature

Visceral transplantation is a broad term encompassing isolated intestine, multivisceral, and any other combination of the visceral allograft with en bloc inclusion of the liver and/or pancreas (Fig. 1). In essence, the intestine is the central core

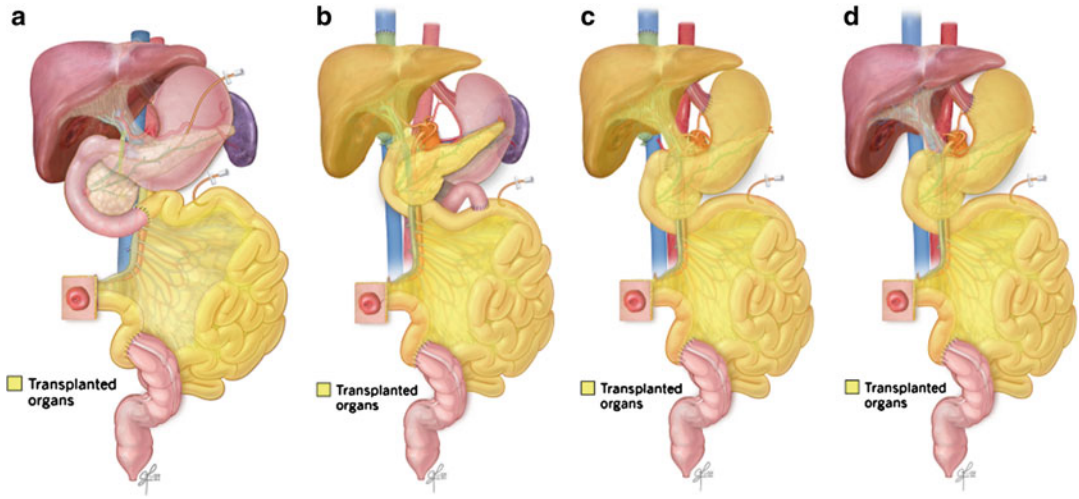


**Fig. 1** The four main visceral allografts. (**a**) Isolated intestine. (**b**) Combined liver-intestine with en bloc pancreaticoduodenal complex. (**c**) Full multivisceral. (**d**) Modified multivisceral. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

of any visceral allograft and the nomenclature is based upon the type and number of the organs that are transplanted en bloc with the intestine (Abu-Elmagd 2007; Fujiki et al. 2017). The term multivisceral is defined as en bloc implantation of the abdominal visceral organs including the stomach and intestine (Abu-Elmagd 2011). Multivisceral transplantation can be "full" or "modified" including the stomach, duodenum, pancreas, and intestine with and without the liver, respectively (Fig. 1c, d). The donor colon, spleen, and/or kidney can always be retained as secondary organs with any of these allograft types without the need for any further substratification (Fujiki et al. 2017).

## Patient Selection

Despite major advances and continuously improved outcomes, intestinal transplantation is still mainly reserved for patients with irreversible IF who can no longer be maintained on PN (Abu-Elmagd 2015). According to worldwide data collected in the Intestinal Transplant Registry, the most common indication for visceral transplantation in adults remains SBS due to mesenteric ischemia (24%), recalcitrant Crohn's disease (11%), volvulus (8%), and trauma (7%) (Grant et al. 2015). Other frequent underlying pathology for visceral transplantation includes abdominal tumors (13%) such as Gardner's syndrome and motility disorders (11%) such as enteric dysmotility, primary hollow visceral myopathy or neuropathy, total intestinal aganglionosis, and secondary chronic intestinal pseudo-obstruction (Grant et al. 2015). Recently emerging indications for visceral transplantation are gut failure after bariatric surgery and diffuse portomesenteric venous thrombosis in patients with liver failure (Abu-Elmagd et al. 2017).

In conjunction with approving reimbursement for the procedure, CMS defined failure of PN and developed criteria for intestinal transplant, as outlined in the below list (Abu-Elmagd et al. 2002; Buchman et al. 2003).

**List of Indications for Intestinal Transplant**

*Failure of PN* (Abu-Elmagd et al. 2002)

1. PN-induced liver injury
   (a) Impending liver failure
      – Bilirubin above 3–6 mg/dL,
      – Progressive thrombocytopenia
      – Progressive splenomegaly
   (b) Overt liver failure
      – Portal hypertension
      – Hepatosplenomegaly
      – Hepatic fibrosis or cirrhosis
2. Central venous access device-related thrombosis of two or more central veins
3. Frequent central-line infection
   1. ≥2 episodes/year of systemic bacteremia requiring hospitalization
   2. Single episode of line-related fungemia
   3. Septic shock and/or acute respiratory distress syndrome
4. Frequent episodes of severe dehydration despite IV fluid in addition to PN

*High Risk of Death Attributable to the Underlying Disease* (Buchman et al. 2003)

1. Desmoid tumors associated with familial adenomatous polyposis
2. Congential mucosal disorders
3. Ultrashort bowel syndrome
   (a) Gastrostomy
   (b) Duodenostomy
   (c) Residual small bowel 10 cm in infants and 20 cm in adults

*Intestinal Failure with High Mortality and Low Acceptance of PN* (Buchman et al. 2003)

1. Intestinal failure with high morbidity or inability to function
   (a) Frequent hospitalization
   (b) Narcotic dependency
   (c) Pseudo-obstruction
   (d) High output stoma
2. Patient unwillingness to accept long-term PN (i.e., young patients)

Specific indications for intestinal transplant including IF-associated liver disease, recurrent catheter-related sepsis, and extensive vascular thrombosis limiting IV access have not changed over time (Grant et al. 2015). In addition to PN failure, nutritional failure is also considered a legitimate indication for transplantation. Nutritional failure is a new term that encompasses development of PN-related life-threatening conditions,

presence of ultra SBS, or diagnosis of end-stage GI disorders not amenable to medical and surgical rehabilitative measures (Hashimoto et al. 2015).

Early referral of patients meeting any of the conditions for visceral transplantation is critical, especially for those suffering PN-induced liver injury. Patients awaiting a combined liver-intestine transplant have higher mortality rate than those awaiting a liver transplant alone (Fryer et al. 2003). Early transplantation before development of nutritional failure or progression of complex abdominal pathology is commonly associated with positive outcome including preservation of the native liver and improved quality of life (Abu-Elmagd et al. 2012; Abu-Elmagd 2014). A 2009 report of 500 visceral transplants showed that PN use for <1 year pretransplant was a favorable predictor of improved survival after transplant (Abu-Elmagd et al. 2009b). Furthermore, the current survival after intestinal transplantation is comparable to that of patients with PN-dependent IF, despite the primary use of the procedure as a rescue therapy (Abu-Elmagd 2006).

Significant cardiopulmonary insufficiency, incurable malignancy, persistent life-threatening intra-abdominal or systemic infections, and severe immune deficiency syndromes with inability for prior successful stem cell transplantation are absolute contraindications to visceral transplantation (Abu-Elmagd et al. 2002, 2017). Lack of adequate social support is considered a relative contraindication due to poor long term survival and all efforts should be made to re-establish functional social support prior to transplant consideration (Abu-Elmagd et al. 2012). The presence of long-standing, controlled neuropsychiatric disorders should not preclude transplantation as successful rehabilitation postvisceral transplantation has recently been documented (Abu-Elmagd et al. 2012). Similarly, a history of GI malignancy, loss of central venous access, and older age are not absolute contraindications for transplant and should be considered on an individual basis within the context of the full evaluation.

## Transplant Evaluation

Prompt referral of all IF patients to a center for gut rehabilitation and transplant may accomplish a two-fold objective: to explore opportunities for rehabilitation while capturing the critical window of opportunity for successful transplantation (Fishbein and Matsumoto 2006). Evaluation of the patient as a transplant candidate begins when all available medical and surgical options have been exhausted. The visceral transplant evaluation process is very similar to that of surgical rehabilitation (see ▶ "Recent Evolution of Gut Rehabilitation" chapter), with an added focus on establishing irreversible IF, determining organ requirements, and reviewing immunologic status. All transplant candidates are thoroughly educated and consented by the transplant nurse coordinator prior to undergoing comprehensive consultation with the multidisciplinary team. An in-depth biochemical analysis is also conducted on all candidates to assess nutritional, hepatic, renal, hematologic, and immunologic status as outlined in Table 1.

The anatomic and functional assessment of the GI tract and of the other organs is highly specialized, guided by the etiology of intestinal failure and clinical manifestations of extra-intestinal diseases.

**Table 1** Visceral transplant evaluation

| Component | Clinical data |
|---|---|
| Past medical history | • Smoking, alcohol, drug abuse<br>• Heart disease, vascular disease, pulmonary disease, renal disease, diabetes<br>• Liver disease, line infections, thrombosis of major central veins |
| Past surgical history | • Operative and pathology reports<br>• Prior surgical consultations |
| Gastrointestinal symptoms | • Nausea, vomiting<br>• Abdominal pain, distention<br>• Diarrhea, constipation |

(*continued*)

**Table 1** (continued)

| Component | Clinical data |
|---|---|
| Laboratory testing | • Nutrition panel<br>• Hypercoagulable panel<br>1. Hematologic studies: protein C, protein S, antithrombin III, anticardiolipin antibodies, lupus anticoagulant, antiphospholipid antibodies and total homocysteine serum levels<br>2. Genetic testing: factor II, factor V Leiden, prothrombin G20210A, and JAK-2 gene mutations<br>• Immune function panel/Hepatic serologies<br>• Anti-HLA antibodies<br>• Toxic drug screening<br>• Tumor markers |
| Gut anatomy and functions | • Radiologic imaging<br>• Endoscopic instrumentation<br>• Histologic examination<br>• Motility testing<br>1. Esophageal, antroduodenal, and anorectal manometry<br>2. Four-hour nuclear medicine gastric emptying studies: liquid and solid phase<br>3. Wireless motility capsule testing<br>4. Defecography and sitz marker testing |
| Status of native liver | • Radiologic imaging: CT abdomen, US liver<br>1. Hepatic steatosis, hepatomegaly, splenomegaly<br>2. Patency of hepatic vessels and biliary system<br>3. Degree of portal hypertension<br>4. Liver volumes<br>• Endoscopic instrumentation<br>1. EGD: esophageal, gastric duodenal varices<br>2. Colonoscopy: rectal varices<br>• Liver biopsy<br>1. Degree of cholestasis, steatosis, fibrosis, cirrhosis |
| Assessment of pancreatic function | • Insulin requirement<br>• Amylase/lipase levels<br>• Peptide-C level<br>• HgA1C |
| Cardiopulmonary and vascular systems | • EKG, Echo, Cardiac stress test<br>• CXR, CT chest, pulmonary function tests<br>• Central vein mapping<br>1. Bilateral upper and lower duplex US<br>2. Bilateral upper and lower venograms<br>• Mesenteric vascular supply<br>1.Visceral angiogram with superior mesenteric and splenic arterial injections with venous phases |
| Health Assessment | • Bone health<br>1. Bone densitometry: Osteopenia, osteoporosis<br>2. Parathyroid hormone (PTH), Vitamin D25 dihydroxy<br>3. Endocrinology consult<br>• Breast, gynecologic and prostate health<br>• Dental health |
| Multidisciplinary transplant team consultations | • Surgical<br>• GI/nutrition<br>• Psychosocial/socioeconomic<br>• Infectious disease<br>• Anesthesia |

For patients with primary enterocyte disease such as radiation enteritis, autoimmune enteropathy, lymphangiectasia, and inflammatory bowel disease, a full radiologic, endoscopic, and pathologic examination of the residual GI tract is essential. Patients with dysmotility and pseudo-obstruction syndrome should undergo GI motility studies to define the type and extent of their disease. Candidates with thrombotic disorders require hematologic studies to identify the underlying hypercoagulable state and abdominal visceral angiography to assess patency of the splanchnic vascular system. In these and other high-risk candidates such as long-term PN-dependent patients, imaging of the upper and lower central veins is essential to establish adequate venous access at the time of surgery. Desmoid tumors should be assessed with a CT angiogram of the abdomen and/or chest to define the extent of the lesion(s) and its relationship to the adjacent vital structures.

An accurate assessment of the extent of PN-associated liver injury is very crucial for successful outcome after transplantation. PN-induced liver disease is frequently under diagnosed and may be present long before elevations in serum transaminases and bilirubin (Chan et al. 1999; Fishbein 2009). The diagnosis of portal hypertension is based upon standard criteria including low blood cell counts, a low platelet count, an enlarged spleen, the detection of gastroesophageal varices or portal hypertensive gastropathy, and the presence of ascites (Abu-Elmagd 2008). Some of these overt manifestations are less pronounced in patients with SBS due to reduced or absent mesenteric arterial flow. All transplant candidates on long-term PN independent of biochemical evidence of liver injury should undergo liver biopsy either at the time of prior attempt for surgical rehabilitation or during the transplant evaluation. A transjugular liver biopsy with bilateral upper and lower venograms may be performed simultaneously in interventional radiology to assess patency of the central venous system. In addition, a computed tomography (CT) of the abdomen with IV contrast is needed to provide imaging of the hepatic vessels, assess degree of portal hypertension, and determine coexistence of any other abdominal organ diseases.

## Types of Visceral Transplantation

There are fundamentally four types of gut transplantation: isolated small bowel transplant, liver-small bowel transplant with pancreas en bloc, multivisceral transplant, and modified multivisceral transplant (Table 2). Transplantation with different combinations of en bloc abdominal visceral organ replacement has been used successfully in patients with various end-stage GI disorders (Abu-Elmagd et al. 2002). Patients with chronic IF are candidates for intestinal transplant either alone, combined with liver and/or pancreas, or as part of a multivisceral graft. The type of transplant required depends on the underlying etiology of IF, quality of the native organs, presence/severity of liver disease, and history of prior abdominal surgeries. In all cases, a vent chimney or simple loop ileostomy is performed to monitor graft rejection and provide easy access for frequent surveillance endoscopy with random mucosal biopsies. Surgical closure of these vents is performed 12–24 weeks after transplantation guided by the postoperative course and functional recovery of the intestinal graft. Gastrostomy and jejunostomy tubes may also be inserted immediately following transplant for postoperative decompression and early enteral feeding.

The general indications for all types of visceral transplantation are outlined in Table 2. When native hepatic functions are preserved, most patients with irreversible IF undergo isolated intestinal transplantation (Fig. 1a). In patients with concomitant failure of other organs, such as those with insulin-dependent diabetes (beta cell failure) and/or end stage renal disease, the pancreas and/or kidney is procured en bloc and simultaneously transplanted with the intestinal allograft. The decision to perform simultaneous hepatic replacement is very challenging, particularly in patients with asymptomatic portomesenteric venous thrombosis and significant liver damage. In general, patients with modest portal hypertension including mild splenic enlargement, platelet count >50,000, no gastroesophageal varices, and portal fibrosis without significant hepatic

**Table 2** Types of allografts

| Transplant procedure | Organs included | Indications |
|---|---|---|
| Isolated intestinal | Intestine +/− colon, kidney, pancreas | Intestinal failure *without* severe PN-induced liver disease |
| Combined liver and intestine | Liver, pancreatico-duodenal complex[a], intestine +/− colon, kidney | Intestinal failure *with* severe PN-induced liver disease |
| Full multivisceral[b] | Stomach, duodenum, pancreas, intestine, liver +/− colon, kidney | Diffuse gut disorders such as dysmotility syndromes, intraabdominal tumors that require extensive evisceration, massive gastrointestinal polyposis, traumatic loss of the abdominal viscera, or portomesenteric venous thrombosis with hepatic decompensation |
| Modified multivisceral[b] | Stomach, duodenum, pancreas, intestine +/− colon, kidney | Preserved hepatic functions in patients with diffuse gut disorders |

[a]Pancreas and duodenum are included in the liver-intestine transplant block for surgical technical reasons, as they share the same axial blood supply with liver and intestine
[b]With possible preserved native pancreaticoduodenal complex and/or spleen

cholestasis should be cautiously considered for intestinal transplantation alone.

A composite liver-intestinal allograft with en bloc pancreaticoduodenal complex is reserved for patients with irreversible liver damage and irreversible IF (Fig. 1b). The procedure should also be considered for patients with liver failure and concomitant thrombosis of the portomesenteric venous system. Criteria for a combined liver-intestine transplant include documented end-stage hepatic disease associated with refractory ascites, spontaneous bacterial peritonitis, refractory variceal bleeding, chronic encephalopathy, hepatorenal syndrome, failure to thrive, and a severe compromise in quality of life (Abu-Elmagd et al. 2001). Additionally, posttransplant survival rates are higher for combined liver-intestine recipients compared with isolated intestine recipients due to proven immunologic benefits of the liver (Abu-Elmagd et al. 2009b).

Full or modified multivisceral transplantation is the only available treatment for patients with irreversible failure of their abdominal visceral organs including the small bowel (Fig. 1c, d) (Hashimoto et al. 2015). It is indicated for symptomatic extensive thrombosis of the splanchnic vascular system, massive GI polyposis or other premalignant neoplasms, and generalized GI dysmotility syndromes. In patients with gut dysmotility and in select patients with extensive abdominal desmoid tumors, the native pancreaticoduodenal complex, including the spleen, may be preserved during a full or modified multivisceral transplant (Fig. 2). Benefits of this include a reduced risk of post-transplant lymphoproliferative disorder (PTLD), elimination of need for biliary reconstruction, and augmentation of islet cell mass with retention of native pancreas (Sogawa et al. 2017; Cruz et al. 2010, 2011).

Inclusion of the donor colon is an option for patients with prior total proctocolectomy and preserved internal and external anal sphincters deemed suitable candidates for a pull-through operation (Fig. 3) (Abu-Elmagd et al. 2017). In a review on colon inclusion in the intestinal graft, improvement was noted in quality-of-life indicators, stool patterns, fecal continence, and parenteral nutrition weaning in recipients of colonic inclusion (Matsumoto et al. 2011). The authors concluded that colon inclusion has no adverse effects and may provide necessary physiologic functions of water absorption, residue breakdown, and storage. The Intestinal Transplant Registry (ITR) has also reported that inclusion of the colon had no adverse effect on survival and those with a donor segment of colon had a 5% higher rate of independence from supplemental PN than visceral transplant recipients without donor colon (Grant et al. 2015).

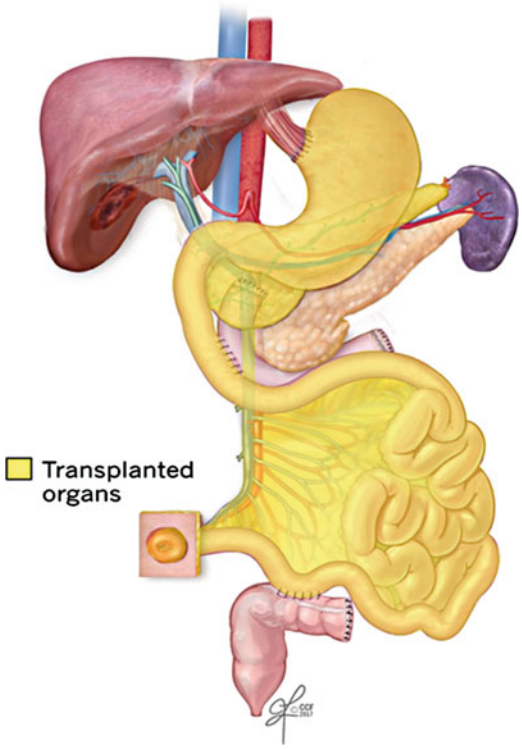


**Fig. 2** Modified multivisceral transplantation with preservation of the native spleen and pancreas. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

## Recipient Surgical Technique

In addition to modification of the donor procedure with inclusion of different donor visceral organs, innovation of the recipient operation has been one of the landmarks of the recent evolution of visceral transplantation. Modifications to both the vascular and gastrointestinal reconstruction operations have been largely driven by organ shortage in the milieu of patients with complex abdominal pathology.

## Vascular Reconstruction

The arterial inflow of the isolated intestinal graft is restored by anastomosing a free donor arterial segment, mostly iliac or carotid, to the recipient infrarenal abdominal aorta or iliac arteries particularly in patients who are undergoing retransplantation with an isolated intestinal graft (Fig. 4). The technique of anastomosing a vascular conduit to the recipient vessels rather than to the allograft mesenteric vessels on the back table avoids difficult exposure and possible prolongation of the warm ischemia time (Abu-Elmagd et al. 2000). In addition, the initial in situ placement of a free donor arterial and venous conduit facilitates a safe vascular reconstruction before bringing the visceral allograft to the operative field (Abu-Elmagd et al. 2000). The venous drainage depends primarily on the technical feasibility of gaining access to the recipient portomesenteric axis. Portal venous drainage (Fig. 4) should always be attempted in patients with inadequate hepatopetal portal flow, previous splenectomy, de-arterialized native liver, and those with caval filters. The systemic caval drainage is used in patients with frozen hepatic hilus, portal vein thrombosis, significant hepatic fibrosis, and prior intestinal transplant (Fig. 4).

The different types of vascular reconstruction of the composite visceral allograft are depicted in Fig. 5a. Nonetheless, the most commonly used arterial vascular reconstruction is the Carrel patch technique utilizing an arterial conduit that is anastomosed to the common aortic patch that contained the orifices of the celiac trunk and superior mesenteric artery (Fig. 5b). For the combined intestinal and pancreas transplantation, a bifurcated aortic graft is commonly utilized on the back table and anastomosed to the superior mesenteric and splenic arteries of the allograft (Fig. 5c). The venous reconstruction of the liver contained visceral allograft is through the common confluence of the native hepatic veins utilizing the piggyback technique (Fig. 6). In recipients with retained native left upper quadrant organs, a portocaval shunt is performed between the retained short segment of the native portal vein and inferior vena cava (Fig. 6). It is important to emphasize that the standard retrohepatic caval replacement is rarely needed and the previously adopted porto-portal shunt is no longer practiced at our center (Fig. 6). With the liver-free composite visceral graft, the venous drainage is commonly portal and similar to the isolated intestinal

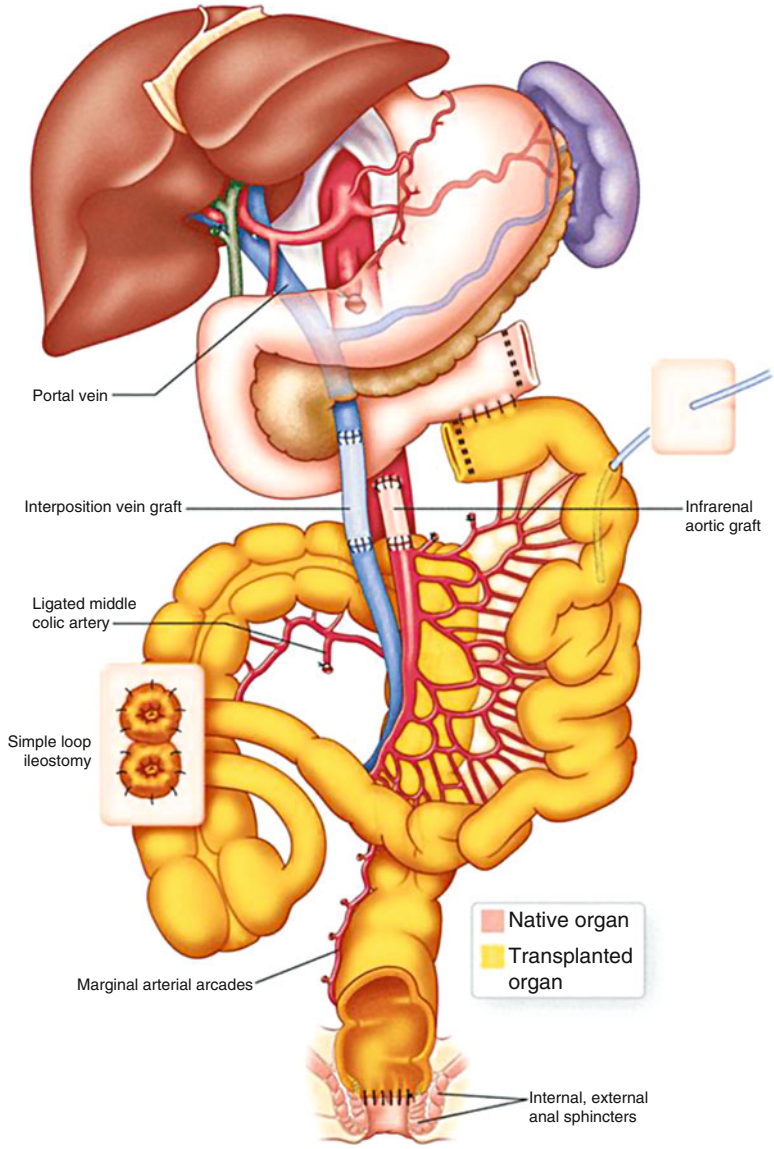


**Fig. 3** Pull through reconstruction with en bloc colon and intestinal transplantation in a patient with intact anal sphincters. (Nyabanga C, Kochhar G, Costa G, et al. Management of Crohn's disease in the new era of gut rehabilitation and intestinal transplantation. Inflamm Bowel Dis 2016; 0:1-14, by permission of Crohn's & Colitis Foundation of America, Inc.)

allograft utilizing the short segment of the donor portal vein to drain the contained organs including the stomach, duodenum, pancreas, and the intestine.

## Gut Reconstruction

Restoration of gastrointestinal continuity is generally achieved using conventional surgical techniques. With isolated intestinal and combined liver-intestine transplantation, the proximal anastomosis is performed between the native duodenum or jejunum and the allograft jejunum with different anastomotic techniques (Fig. 7a–c). In selected cases with ultra-short duodenum, a native colonic conduit is utilized for reconstruction to avoid the need for a more composite allograft (Fig. 7d). With full or modified multivisceral transplantation, foregut reconstruction involves anastomosing the transplanted stomach to the native esophagus or the residual gastric cuff (Fig. 1c, d). In addition, a pyloromyotomy or pyloroplasty is required to drain the denervated allograft stomach.

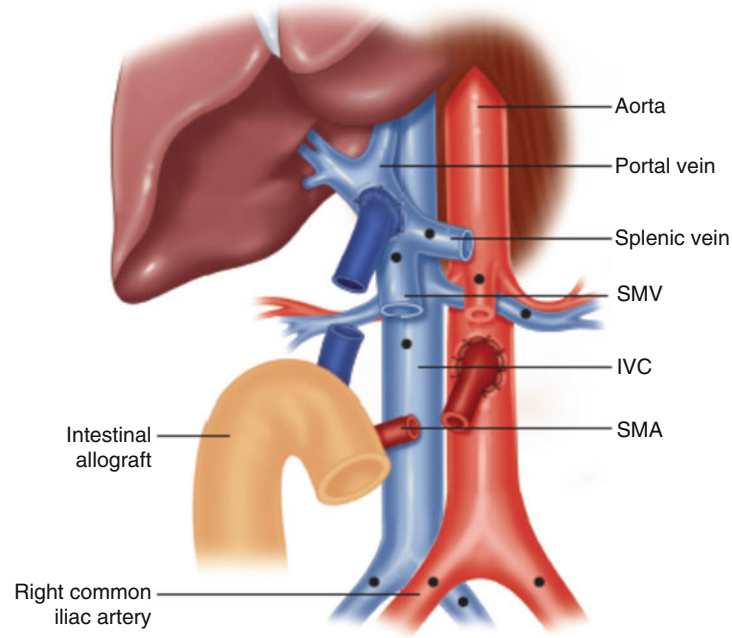


**Fig. 4** Arterial and venous vascular reconstruction of the intestinal allograft. Early in situ vascular grafting is performed by anastomosing a free donor arterial and venous vascular graft in the recipient before bringing the intestinal allograft to the operative field. The infrarenal aorta or common iliac artery (CIA) is used for the arterial inflow. The portal vein (PV), superior mesenteric vein (SMV) or splenic vein (SV) is used for portal venous drainage and the inferior vena cava (IVC) for systemic drainage. The multiple options are labeled with *black dots*

A piggyback duoduodenal anastomosis is also required for patients with preserved native duodeno-pancreatic complex (Fig. 2). Distal gut reconstruction is restored in patients with residual hindgut by anastomosing the allograft ileum to the native colon or rectum. For endoscopic allograft monitoring, a diverting chimney (Fig. 8a) or simple loop ileostomy (Fig. 8b) is created and an end ileostomy is done in patients with prior proctocolectomy (Fig. 8c).

## Postoperative Management

Immunosuppressive therapy, early diagnosis of allograft rejection, infectious prophylaxis, and nutritional management are the primary components of posttransplant care. The introduction of novel immunosuppressive agents and the refinement of immune modulatory strategies have improved the therapeutic efficacy of visceral transplantation. The use of recipient preconditioning with lymphoid-depleting agents combined with posttransplant minimal immunosuppression has led to improved survival with reduced incidence of intractable rejection, PTLD, and fatal infections.

With no currently available biochemical or biological markers of rejection, surveillance endoscopy with multiple mucosal biopsies is the only tool to diagnose intestinal rejection. Endoscopic findings of mucosal erythema or ulceration and histologic evidence of allograft injury including crypt damage, apoptosis, and sloughing of the intestinal mucosa may be seen with acute rejection. Clinical signs of acute rejection may include fever, diarrhea or high stoma output, abdominal distention, leukocytosis, thrombocytopenia, or GI bleeding. With chronic rejection, recipients may present with weight loss, severe malnutrition, GI bleeding, bowel obstruction, and enterocutaneous fistulae with full-thickness histopathologic evidence of cryptopenia, obliterative arteriopathy, mesenteric sclerosis, and lymph node depletion. Increasing dosing of immunosuppression with steroids and antilymphoid preparations is required for treatment of acute rejection, and advanced chronic rejection may be treated with allograft enterectomy and/or retransplantation.

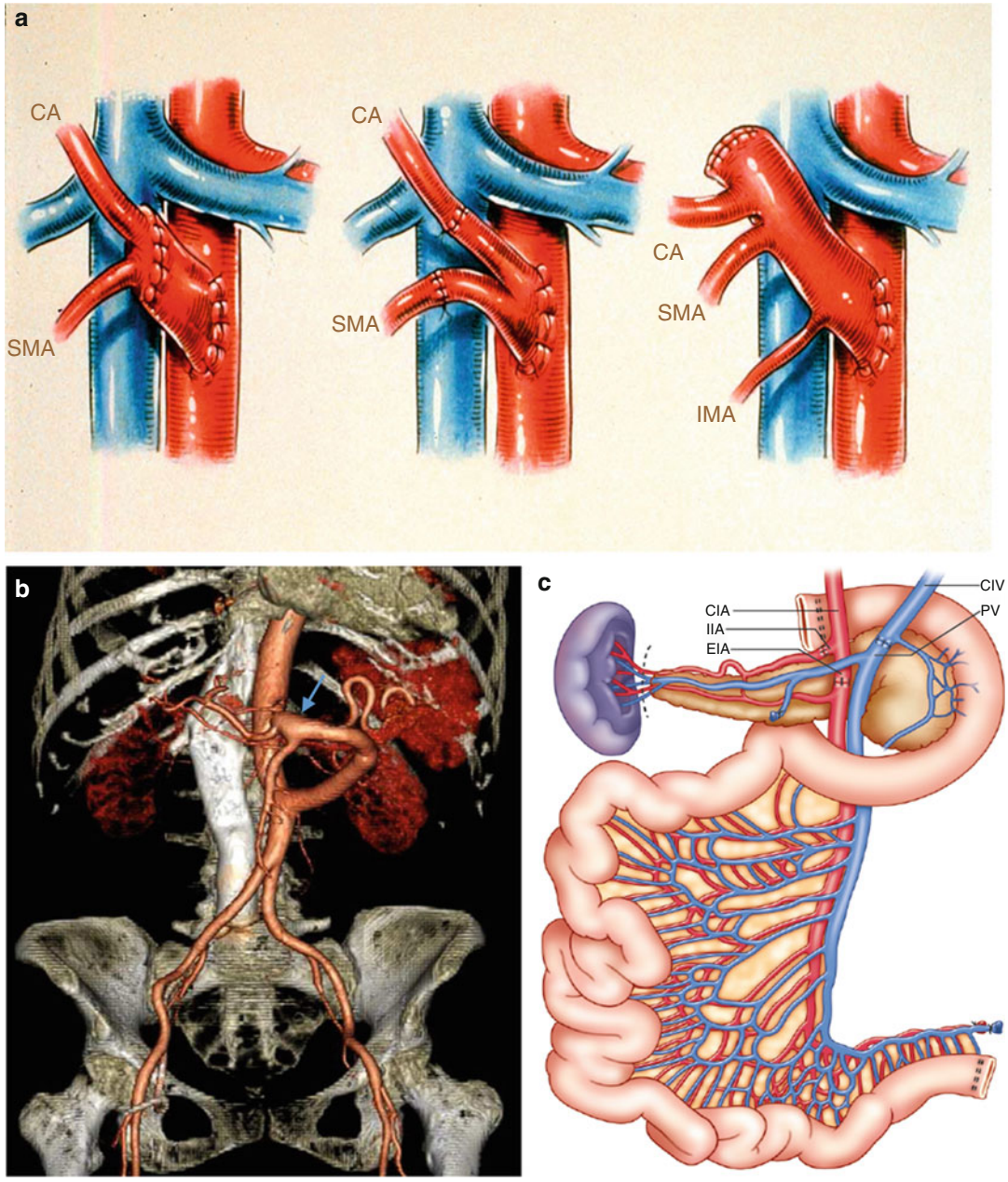


**Fig. 5** (**a**) The different types of vascular reconstruction of the composite visceral allograft. CA: celiac artery, SMA: superior mesenteric artery, IMA: inferior mesenteric artery. (**b**) A 3-D reconstruction of CT angiogram in a multivisceral recipient. Note the Carrel-patch reconstruction (arrow) that was performed on the back table containing both the celiac and superior mesenteric origin. (**c**) En bloc retrieval of the intestine and pancreas with back table vascular reconstruction. Splenectomy and ligation of the bile duct stump are also performed as part of the back-table procedure. Placement of an interposition vein graft is not needed. CIA: common iliac artery, CIV: common iliac vein, IIA: internal iliac artery, EIA: external iliac artery, PV: portal vein. (Adapted with permission from Abu-Elmagd, K., Bond, G., Reyes, J. et al. Intestinal transplantation: a coming of age. Adv Surg. 2002; 36: 65–101)

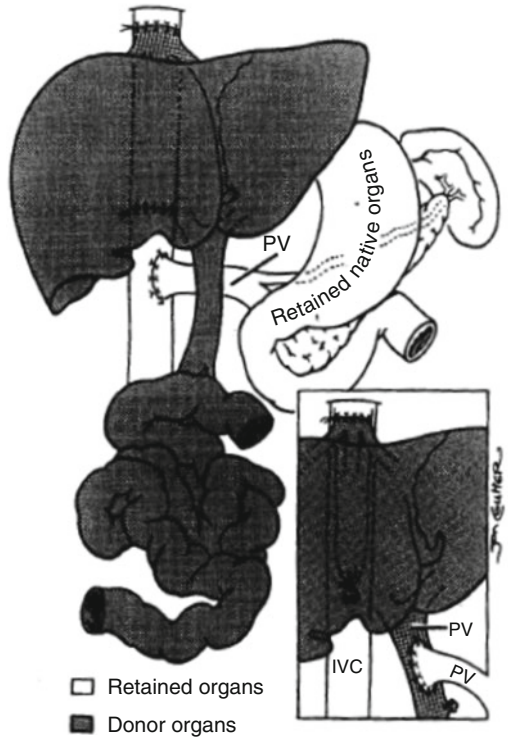


**Fig. 6** Drainage of the venous outflow of the retained native viscera in liver-intestinal recipients into their inferior vena cava (IVC) by portocaval shunt. The previously adopted porto-portal shunt (inset) is no longer practiced at our center. (Used with permission of Starzl TE, Todo S, Tzakis A, et al. The many faces of multivisceral transplantation. Surg Gynecol Obstet 1991;172:335–44. *Surgery, Gynecology, & Obstetrics* is now known as the *Journal of the American College of Surgeons*; Buchman et al. 2003)

As part of the two-way immune interaction, the incidence of graft-versus-host disease (GVHD) in isolated intestinal transplantation is reported to be less than 10% (Clouse et al. 2017). Higher rates are seen in composite visceral allograft recipients, particularly in children with immunodeficiency, and in those who had splenectomy or were pretreated with antilymphocyte-depleting agents (Abu-Elmagd et al. 2017). The disease commonly involves the recipient's skin and gastrointestinal tract and is confirmed with histopathologic examination of the affected organ(s) and detection of circulating donor cells in the peripheral blood of the recipient.

Management of infectious complications has gradually been enhanced as the result of cumulative clinical experience, advances in molecular diagnostic techniques, and availability of new antimicrobial drugs. The clinical availability of the quantitative competitive polymerase chain reaction (PCR) assay triggered serial monitoring of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) load in peripheral blood. Treatment strategies include prophylactic antibiotics, preemptive therapy of EBV and CMV viremia, and active treatment of bacterial and fungal infections. These management protocols, along with minimization of posttransplant immunosuppression, have significantly reduced risk and mortality of PTLD, CMV, and microbial infections.

The ability to restore nutritional autonomy and graft function is the second most important indicator of successful visceral transplantation after survival. Assessment of graft function is accomplished through careful serial clinical, biochemical, and nutritional assessments (Abu-Elmagd et al. 2001). When transplantation is effective, most recipients tolerate oral feeding within the first 2 weeks of surgery. Within 4 weeks, PN and supplemental IV fluids are commonly discontinued with achievement of full nutritional autonomy. The failure to achieve full recovery of GI function, particularly gut motility and fat absorption, may be the result of denervation and lymphatic disruption of the intestinal allograft, respectively (Rovara et al. 2003).

Bacterial and fungal overgrowth is also a common finding in the intestinal allografts brought about by change in the ecology of the intestinal flora. Proposed mechanisms for altered gut microbiota include surgical manipulations, absence of the ileocecal valve, disruption of the intestinal lymphatics, impaired host defenses due to heavy immunosuppression, gut dysmotility, preservation injury, rejection, or PTLD (Abu-Elmagd et al. 2001). Further study is needed to plot dynamic changes in the intestinal allograft microbial ecology and its potential influence on allograft graft function, rejection, and survival (Abu-Elmagd 2015).

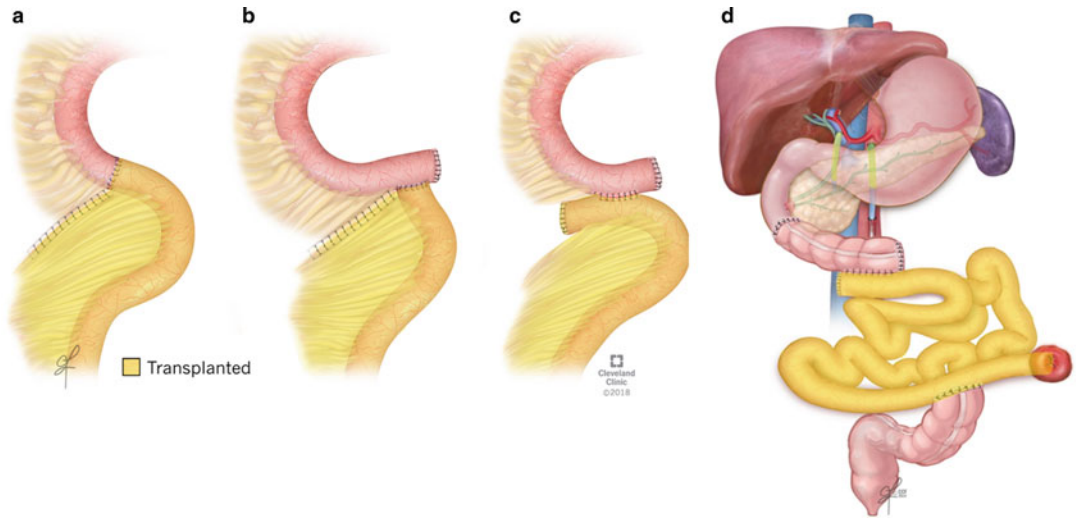


**Fig. 7** Gastrointestinal Reconstruction. Proximal allograft jejunum is anastomosed to the retained short segment of native jejunum in an (**a**) end-to-end, (**b**) end-to-side, or (**c**) side-to-side fashion. Foregut reconstruction with (**d**) interposition segment of the native colon. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

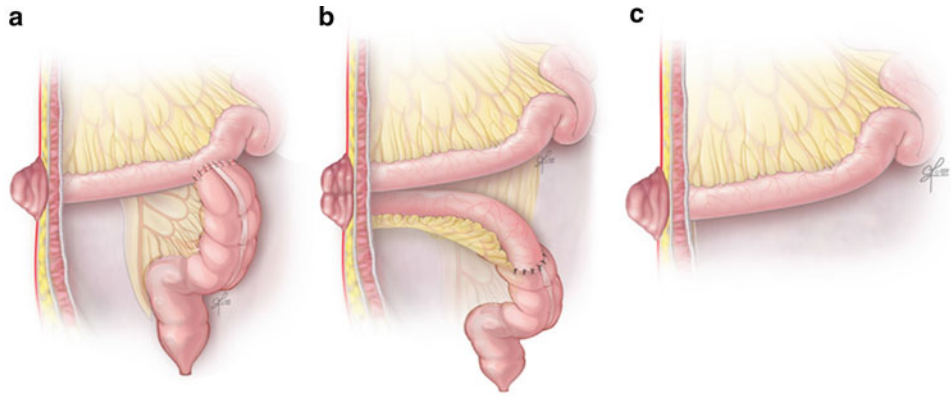


**Fig. 8** Hindgut reconstruction with creation of a (**a**) chimney ileostomy, (**b**) simple loop ileostomy, or (**c**) end ileostomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography. Copyright 2009–2018. All Rights Reserved; Buchman et al. 2003)

## Long-Term Outcomes

The survival outcome of visceral transplantation has significantly improved over the last few decades. According to the Intestinal Transplant Registry (ITR), there is compelling evidence that the 5-year patient and graft survival has significantly improved (Fig. 9a) (Grant et al. 2015). Similar results have been documented by the Pittsburgh largest single center experience with the longest follow-up worldwide (Fig. 9b) (Abu-Elmagd et al. 2009b). Such an improvement in survival outcome can be partially due to innovative surgical techniques, improved postoperative care, and novel immunosuppressive protocols (Fig. 9b, c) (Abu-Elmagd et al. 2009a). Equally impressive is the Pittsburgh long-term outcome beyond the post-transplant 5 year landmark with

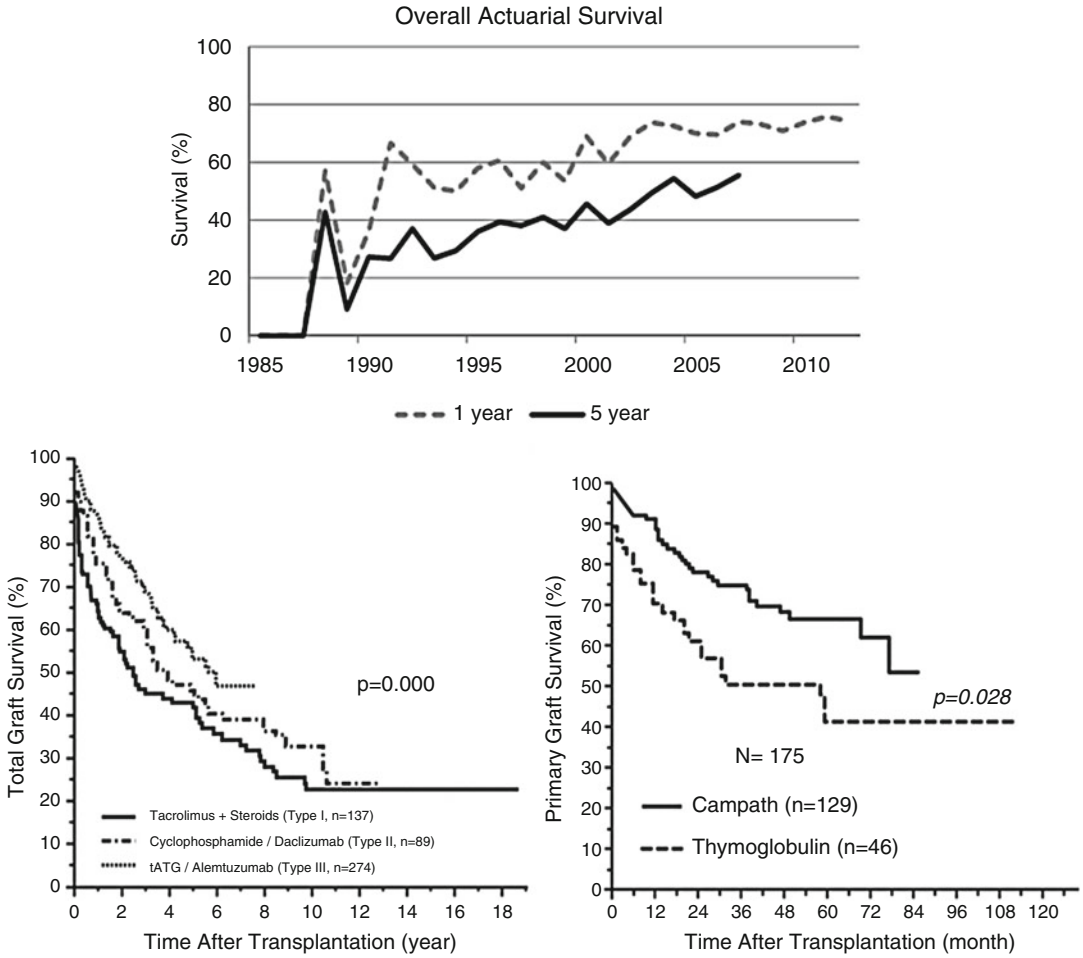


**Fig. 9** (**a**) A times series analysis of the 1- and 5-year actuarial graft survival shows significant improvement over time ($p < 0.001$). (Used with permission of Grant D, Abu-Elmagd K, Masariegos G, et al. Intestinal transplant registry report: Global activity and trends. Am J Transplant 2015;15:210–19); (**b**) improvement of visceral allograft survival according to the type of immunosuppression. (Used with permission of Abu-Elmagd KM, Costa G, Bond GJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg 2009;250(4):567–81); and (**c**) better graft survival in patients pretreated with alemtuzumab (Campath-1H) compared to those pretreated with antithymocyte globulin (thymoglobulin) (Used with permission of Abu-Elmagd KM, Costa G, Bond GJ, et al. A decade of experience with a single dose of rabbit antithymocyte globulin or alemtuzumab pretreatment for intestinal and multivisceral transplantation. Clin Transpl 2012:155–66)

a patient survival rate of 75% at 10 years and 61% at 15 years with a respective graft survival of 59% and 50% (Fig. 10) (Abu-Elmagd et al. 2012). The study also documented the significant risk factors that affect long-term survival as shown in Table 3.

Nutritional autonomy following visceral transplantation is defined as freedom from intravenous nutrition and fluid supplementation with the goal of removing central venous access and eliminating associated complications to thereby restore a more physiologic way of life. With a mean follow up of 10 +/− 4 years, full nutritional autonomy was achievable in 90% of visceral transplant survivors as reported in the Pittsburgh long-term outcome study (Fig. 11a) with a significant and sustained improvement in body mass index (BMI) among the adult population (Fig. 11b). All

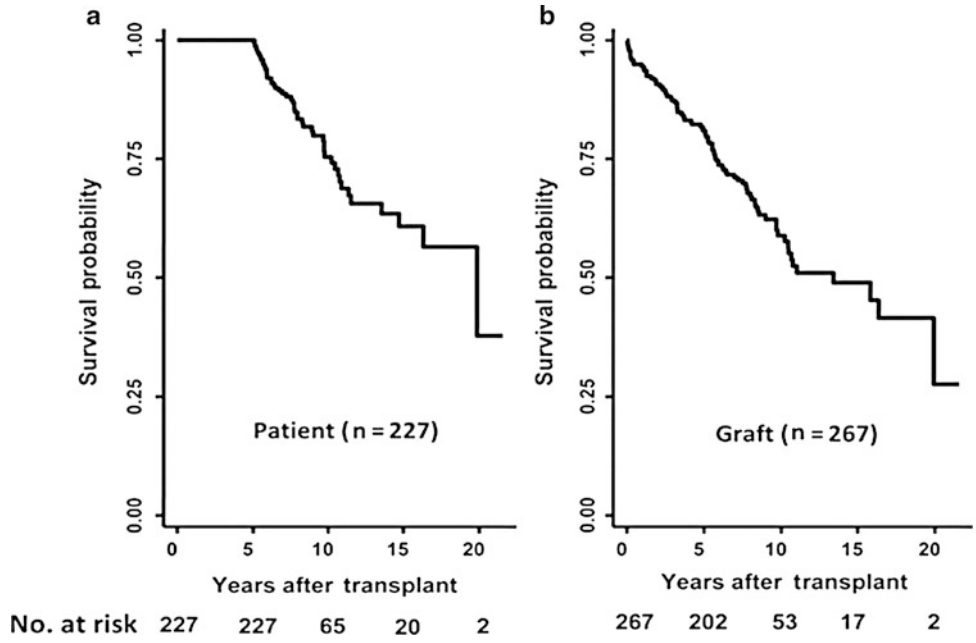


**Fig. 10** Kaplan-Meier survival curves for the 5-year conditional patient (**a**) and graft (**b**) survival after visceral transplantation. (From Abu-Elmagd KM, Kosmach-Park B, Costa G, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg 2012;256(3):494–508, with permission)

**Table 3** Long-Term Patient Survival Risk Factors and Predictors of Graft Failure

| | *P* | Hazard ratio | 95% confidence interval |
|---|---|---|---|
| Patient | | | |
| Lack of social support | 0.000 | 6.132 | 3.370–11.160 |
| Rejection ≤90 day | 0.016 | 2.363 | 1.172–4.765 |
| Female recipient | 0.025 | 1.992 | 1.089–3.646 |
| Recipient age ≥ 20 yr | 0.025 | 2.014 | 1.093–3.711 |
| Retransplantation | 0.026 | 2.053 | 1.089–3.873 |
| No preconditioning | 0.046 | 2.013 | 1.013–4.997 |
| Graft | | | |
| Liver-free allograft | 0.000 | 3.224 | 2.026–5.132 |
| Splenectomy | 0.001 | 2.212 | 1.396–3.506 |
| HLA mismatch | 0.040 | 1.258 | 1.011–1.565 |
| Rejection ≤90 day | 0.046 | 1.601 | 1.008–2.541 |
| PTLD | 0.085 | 1.638 | 0.934–20,872 |

children experienced normal growth except a few who required growth hormone.

With improved survival and nutrition outcome, quality of life has become one of the primary therapeutic end points of visceral transplantation. A few scattered reports have been published within the last 20 years among both children and adults (Sudan et al. 2000, 2002; Ngo et al. 2011; Cameron et al. 2002; Pironi et al. 2006, 2012; Golfieri et al. 2010; O'Keefe et al. 2007). Studies among children undergoing visceral transplantation demonstrated physical and psychosocial functions similar to healthy normal children (Sudan et al. 2002; Ngo et al. 2011). However, the parental proxy assessments were different with lower functional responses in certain

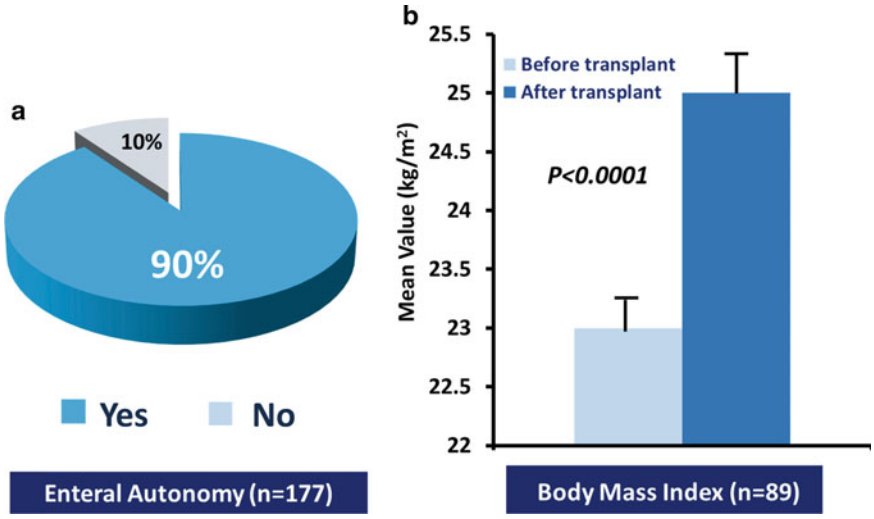


**Fig. 11** Nutritional autonomy after visceral transplantation. (**a**) Achievement of enteric autonomy defined by freedom from intravenous nutrition and fluid supplement. (**b**) Body mass index before and after transplantation. (From Abu-Elmagd, K.M., Kosmach-Park, B., Costa, G. et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Ann Surg. 2012; 256: 494–508, with permission)

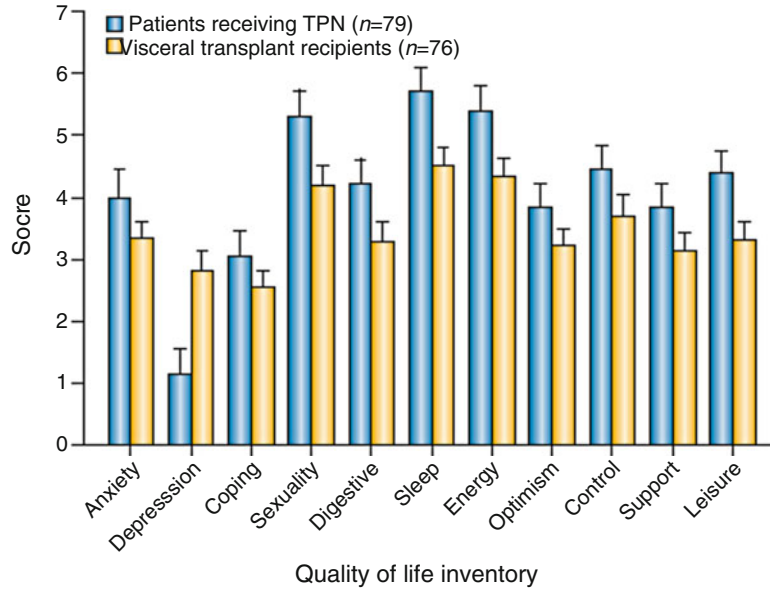


**Fig. 12** Reversal of the depressed effect of PN on most quality of life domains, except depression, after visceral transplantation. (From Abu-Elmagd, K.M., Kosmach-Park, B., Costa, G. et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. *Ann Surg.* 2012; 256: 494–508, with permission)

categories than that given by transplanted children. In addition, lower values in the school functioning subcategories and psychological health summary score were reported compared with healthy children (Ngo et al. 2011). In adults, most published studies on health-related quality of life (HRQOL) have demonstrated improvement in all of the domains except for depression, with better rehabilitative indices than PN (Fig. 12) (Abu-Elmagd et al. 2012).

Socioeconomic milestones have also been used to assess the level of rehabilitation achieved with visceral transplantation in all age groups (Abu-Elmagd et al. 2012). A high education score was reported with sustained cognitive, psychosocial, and physical functions. In addition, the

ability to create a nuclear family along with high Lansky and Karnofsky performance scores is demonstrated and comprehensively reported (Abu-Elmagd et al. 2012). The data have also been in favor of early consideration for visceral transplantation to further improve quality of life by reducing the risk of organic brain-dysfunction-related morbidities associated with brain atrophy, cerebral vascular insufficiency, micronutrient deficiencies, trace element toxicities, and liver-failure (Idoate et al. 1999; Dekaban 1978; El-Tatawy et al. 1983; Kawakubo et al. 1994). Accordingly, early consideration of transplantation is strongly recommended for patients with irreversible gut failure who are not suitable candidates for autologous gut rehabilitation.

## Conclusion

Visceral transplantation has become the definitive treatment for patients with end-stage intestinal failure and life-threatening complications of PN. Advances in surgical technique, immunosuppressive therapy, early identification, and treatment of infection and gains in center experience have led to improved patient and graft survival. Management of the chronic complications of long-term immunosuppression including hypertension, diabetes, renal failure, osteoporosis, and other associated morbid events is important to further successful outcomes. Despite successful treatment, morbidity of long-term immunosuppression remains detrimental to patient care and overall health. Accordingly, efforts to achieve transplant tolerance with drug-free allograft acceptance are essential along with early patient referral and listing for the long-term therapeutic efficacy of intestinal and multivisceral transplantation.

## Cross-References


- ▶ Causes of Short Bowel Syndrome in Adults
- ▶ Modern Parenteral Nutrition
- ▶ Psychosocial Issues in Intestinal Transplantation
- ▶ Recent Evolution of Gut Rehabilitation


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