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Pediatric Small Bowel Transplantation

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Abstract
Purpose of Review Small bowel transplantation is the only currently available option for children with permanent intestinal failure that can allow for full enteral nutrition. The aim of this article is to provide a comprehensive review of the indications, surgical technique, allograft types, perioperative management, and outcomes of children who undergo intestinal transplantation.
Recent Findings Advancements in the management of immunosuppression and associated complications have been the most recent contributor to improved patient outcomes following intestinal transplantation. Most centers have adopted protocols that consist of maintenance therapy with tacrolimus following induction with a steroid bolus and either an IL-2 antagonist, rabbit antithymocyte globulin, or alemtuzumab. Some will eventually convert patients from tacrolimus to sirolimus for long-term maintenance. Improved viral detection methods have allowed for early detection and management of EBV-associated complications including PTLD. Novel methods for early and less invasive detection of acute cellular rejection may allow for decreased morbidity from this complication in the future.
Summary While outcomes following intestinal transplantation have improved, they lag behind those for other solid organ transplants due to the high rate of immunologic complications found in this patient population. Future progress will depend on development of methods for earlier and more accurate detection of rejection, improvements in the detection and management of infection-related complications including PTLD, and on refinements in the management of chronic rejection.

Keywords Pediatric · Small bowel · Transplantation · Intestinal failure

Introduction

Intestinal failure (IF) is defined as the inability of the gastrointestinal tract to meet the nutritional demands to support and maintain the growth and nutrition of children and adults. IF may be caused by a number of disease processes which range in duration from self-limiting illnesses to chronic conditions [1, 2] While the vast majority of cases of chronic IF are secondary to short bowel syndrome (SBS) due to either an inherited or acquired condition, other disease processes such as motility disorders, diseases of the intestinal epithelia, and neoplasms may also result in IF even without physical loss of intestine (Table 1) [2–4]. In a landmark 1968 paper, Dudrick and Rhoads were the first to demonstrate the potential of parenteral nutrition (PN) to maintain normal nutrition and growth of beagle puppies [5]. Soon thereafter, Wilmore and Dudrick reported the first successful use of PN to treat an infant suffering from IF, transforming what was once a uniformly fatal disease into a chronic medical problem [6]. Despite the life-sustaining ability of PN, its long-term use is not without significant complications, such as central venous catheter-associated infections/sepsis, loss of venous

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Table 1 Etiologies of intestinal failure [2–4]

Etiology	Disease	Percentage
Short bowel syndrome	Intestinal atresia, midgut volvulus, gastroschisis, NEC	63
Motility disorder	Long-segment intestinal agangliosis, chronic intestinal pseudo-obstruction	17
Epithelial dysfunction	Microvillous inclusion disease, Crohn's disease, tufting enteropathy	9
Miscellaneous	Familial polyposis, benign and malignant neoplasms, intestinal allograft failure	11

access due to stricture or thrombosis, and PN-associated liver disease [7–9].

These risks, combined, make long-term dependence on PN undesirable and in some cases, unsustainable, making intestinal rehabilitation and the eventual transition to full enteral autonomy of the utmost importance in the care of patients with IF. Although the development of hepatoprotective PN regimens and advancements in the clinical care of IF patients have decreased both the morbidity and mortality associated with chronic PN usage, there remains a subset of patients whose ability to wean from PN remains low. For such patients, who typically have either extremely short residual bowel length or have poor underlying intestinal motility, alternative interventions such as autologous intestinal reconstruction surgery or intestinal transplantation may be required [10••, 11].

Indications and Contraindications for Intestinal Transplantation

Although the first successful experimental intestinal transplants were performed in the 1950s, the first successful human cases were not reported until the late 1980s with the development of cyclosporine and tacrolimus due to the high rate of infectious and immunological complications [9]. Since that time, refinements in organ preservation, immunosuppressive regimens, and perioperative care have all combined to make intestinal transplantation an increasingly safe and effective means of treating select patients with IF.

Intestinal transplantation is currently recommended for those patients who have developed complications related to long-term PN exposure, such as liver failure, extensive thrombosis of two or more major central venous access sites, repeated catheter-associated infections, or frequent episodes of dehydration. Based on these, as well as other clinical metrics, the American Society of Transplantation (AST) and USA Medicare and Medicaid Services have developed a set of approved indications for ITx shown in Table 2 [12–14]. While the optimal timing of transplantation remains an area of active debate, given the high mortality of late referrals and difficulty finding appropriate allografts for children resulting in high waiting list mortality, early referral for transplant evaluation is generally recommended for patients deemed at high risk for failure of PN [15, 16].

Table 2 Indications for small bowel transplant [12–14]

Failure of parenteral nutrition
PN Related Liver Disease
Impending liver failure (total bilirubin 3–6 mg/dL, progressive thrombocytopenia or splenomegaly
Overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis or cirrhosis)
Line Complications
Central venous catheter-related thrombosis of 2 or more central veins
Frequent episodes of central line related sepsis: 2 >/= episodes of systemic sepsis per year; a single episode of line-related fungemia; septic shock or acute respiratory distress syndrome
Failure to Thrive
Recurrent episodes of dehydration despite resuscitation with intravenous fluid in addition to parenteral nutrition
High Disease Related Mortality
Desmoid tumors secondary to familial adenomatous polyposis
Ultra-short bowel syndrome (gastrostomy, duodenostomy, residual small bowel length equal to or less than 10 cm in infants and 20 cm in adults)
Mucosal disorders
High Disease Related Morbidity or Inability to Tolerate PN Dependence
Frequent hospitalizations or narcotic dependency in setting of intestinal failure
Inability to function due to disease-related factors (e.g., pseudo-obstruction, high output stoma)
Patient factors related to unwillingness to accept long-term parenteral nutrition dependence

Recipient Selection

Evaluation for transplantation involves a multidisciplinary team which includes physicians, surgeons, transplant coordinators, nutritionists, social workers, and

psychologists among many others. The medical evaluation is aimed at not only determining the clinical suitability for transplantation, but also assessing the type of allograft required, an overview of co-morbid conditions, and surgical considerations such as vascular access, prior abdominal surgery, and ability to tolerate general anesthesia.

Contraindications to transplantation, which include active or recent malignancy, uncontrolled systemic infections, and severe, uncontrolled medical conditions which would limit the patient's ability to tolerate major abdominal surgery, should be thoroughly investigated during the evaluation process.

Types of Grafts and Operative Technique

The choice of intestinal allograft largely depends upon the underlying disease process, associated congenital anomalies, prior operative history, and the presence of PN-related complications such as liver disease. Generally speaking, intestinal transplantation may be performed using an isolated intestinal graft (ITx) (Fig. 1a) or in combination with other abdominal viscera as part of a combined liver–intestine (LITx) or multivisceral (MVTx) graft (Fig. 1b, c) [17]. More recently, living-donor ITx and LITx have been reported as alternative operative strategies for pediatric patients [18•].

Isolated intestinal grafts are indicated for those patients who have end-stage IF without evidence of additional organ dysfunction. In such cases, the dysfunctional native intestine is removed and replaced with the donor graft. As shown in Fig. 1a, the recipient jejunum is anastomosed to the proximal donor jejunum, thereby restoring intestinal continuity [17]. An end ileostomy is created to allow for frequent endoscopy and biopsy of the intestinal graft. Vascular inflow into the graft is typically obtained via the aorta while venous outflow may be achieved via either the portal vein or inferior vena cava (IVC), with the latter being the preferred method in current practice [19].

First reported in 1990, combined liver–intestine transplantation is reserved for those patients with IF complicated by liver disease [20]. While the initial LITx grafts included only the liver and intestines necessitating the removal of the donor duodenum and pancreas, in current practice, the liver, duodenum, pancreas, and small bowel are transplanted en bloc, thereby preserving the donor hepatic hilum (Fig. 1b) [17]. This method not only avoids the need for complex biliary reconstruction, but has the additional advantage of reducing the risk of vascular and/or biliary complications post-operatively [21]. In LITx, intestinal continuity is achieved by anastomosing the recipient jejunum to the donor jejunum in an end-to-side fashion while the distal small bowel is brought out as an end ileostomy. Typically arterial inflow to the graft is obtained directly from the infrarenal aorta, while venous drainage is achieved following piggybacked anastomosis of the donor hepatic veins to the recipient suprahepatic IVC. As documented in the original report of this procedure, venous drainage of the native stomach, duodenum, pancreas, and spleen is via a native portosystemic shunt [21]. Of note, transplantation of the liver and intestines as separate allografts, without the pancreas, has been reported in the literature. One potential benefit of this method is that a failing intestinal allograft could be removed and re-transplanted without impacting the original transplanted liver [22, 23].

Similar to LITx but additionally including the stomach and occasionally spleen, MVTx is pursued for those patients with IF and liver disease who also require replacement of the stomach and/or duodenopancreatic complex secondary to either vascular involvement of a tumor around the celiac axis or portomesenteric thrombosis [24–26]. MVTx may also be utilized in very small infants or patients in whom there is a notable donor–recipient size

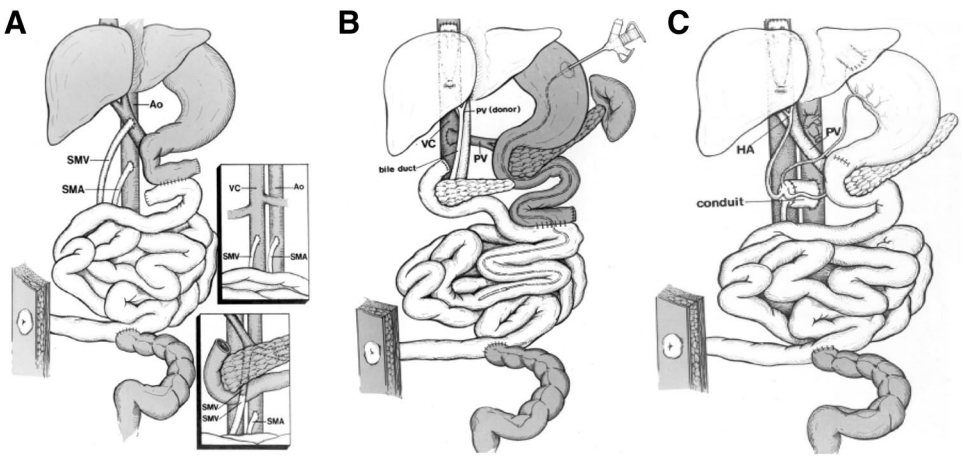

Fig. 1 Types of intestinal allografts [17], **a** isolated intestinal allograft. **b** Combined liver–intestine graft, with donor duodenum and pancreas. **c** Multivisceral allograft, with donor organs including stomach, liver, duodenum, pancreas, and small bowel (Copyright © 2016, Springer-Verlag Berlin Heidelberg. Reprinted with permission.)

discrepancy, as MVTx mandates removal of more native organs thereby making more space for the allograft [19]. As seen in Fig. 1c, proximal gastrointestinal continuity is restored via an anastomosis of the donor and recipient gastric fundus, while distally, an end ileostomy is again created to allow for endoscopic surveillance of the intestinal graft [17]. Pyloroplasty is performed in all cases due to lack of vagal innervation to the transplanted stomach. Arterial inflow is achieved by use of a donor thoracic aortic interposition graft from the recipient infrarenal aorta to the donor aorta which includes both the celiac and superior mesenteric arteries. Venous drainage is established as described for LITx above.

Living kidney and liver donation have been shown to decrease time to transplantation as well as minimize cold ischemia time resulting in improved graft and patient [27, 28]. Living-donor intestinal transplantation has been reported by several centers in both adult and pediatric patients to reasonable outcomes. First described by Gruessner and Sharp in 1997, the indications for living-donor intestinal transplantation remain the same as those utilizing deceased-donor allografts [29]. In this procedure, the donor bowel is measured from the Ligament of Treitz to the ileocecal valve (ICV). From this, 150–180 cm of bowel is resected, starting approximately 20 cm from the ICV, and only after repeated measurement ensures that the donor is left with at least 60% of their original small bowel length [18•]. The terminal branches of the superior mesenteric artery and vein are identified, ligated, and ultimately anastomosed in an end-to-side fashion to the aorta and IVC, respectively, to establish vascular inflow and outflow to the intestinal graft. Intestinal continuity is restored proximally by anastomosis to the recipient duodenum and distally to the remaining colon in a functional end-to-end manner [30]. As with the procedures described above, an ileostomy is then fashioned for endoscopic access and evaluation of the graft.

Post-operative Care

Surgical Complications

As with transplantation of other solid organs, bleeding, arterial or venous thrombosis, anastomotic leak, and bowel perforation or obstruction are all possible complications which may arise in the immediate post-operative period. Although technical complications following intestinal and multivisceral transplantation were initially very high in early reports of these procedures, complications have most recently been estimated to be around 7–8% in one large series due to in large part to advancements in surgical technique and posto-perative care [31].

Nutrition

While the primary goal of intestinal transplantation is to restore normal function of the gastrointestinal tract, there remains no standard protocol across centers for weaning PN and initiating enteral nutrition. Generally speaking, most programs aim to initiate enteral feeds once there is evidence of bowel function, which generally occurs 3–14 days following transplantation [32, 33]. As enteral nutrition is important in the stimulation of gut hormones, early feeding with continuous, low-volume feeds is an important consideration in restoring gut health [34]. While choice of formula varies across institutions, feeds high in long chain triglycerides are generally avoided for multiple weeks post-transplant due to manipulation and presumed alteration of mesenteric lymphatic channels [22, 35•].

Although many children are able to fully wean from PN within weeks following transplant, most have significant oral aversion and may require enteral tube feeding support for years post-operatively, making long-term enteral access of critical importance in this population [33, 36].

Immunosuppression

While the discovery and widespread use of cyclosporine and tacrolimus made intestinal transplantation a feasible option for patients with IF as early as the late 1980s, morbidity and mortality remained high due to acute and chronic rejection as well as medication-related side-effects [9]. Since that time, advancements in our understanding of allo-engraftment as well as the formulation of antibody-based immunosuppressive drugs have combined to create a relatively standardized immunosuppressive regimen for patients undergoing intestinal transplantation. In current practice, most patients receive induction therapy with a single steroid bolus in addition to an IL-2 blocking agent, rabbit antithymocyte globulin (rATC), or alemtuzumab (Campath). Maintenance therapies primarily consist of tacrolimus used alone or in conjunction with additional agents such as mycophenolate mofetil and/or steroids.

Interestingly, in 2012, Trevizol et al., reported a literature review of induction and maintenance protocols at major intestinal transplant centers between 2006 and 2010 [37]. This series highlighted three standard protocols, with Protocol 1 consisting of daclizumab induction and tacrolimus/steroids for maintenance, Protocol 2 utilizing alemtuzumab for induction and tacrolimus for maintenance, and finally Protocol 3 which included thymoglobulin and rituximab for induction and tacrolimus for maintenance. While Protocol 2 demonstrated the best outcomes in terms of rates of acute cellular rejection (ACR) at 34% as compared to 54% (Protocol 1) and 48% (Protocols 3), Protocol 3 performed the best at balancing ACR with risk of

infection, which was found to be 62.5, 52, and 7.4% for Protocols 1, 2, and 3, respectively [37].

Rejection

Although major advancements in immunosuppressive therapies have helped to mitigate the risk of ACR following intestinal transplantation, ACR remains one of the most common causes of death post-transplant and is found in as many as 50% of pediatric patients undergoing ITx [38, 39].

Diagnosed via a combination of clinical symptoms (diarrhea, bloody stoma output, abdominal pain, and fever), endoscopy, and mucosal biopsies, ACR typically presents within the first three months post transplant, although late presentations have been reported in the setting of non-compliance or inadequate immunosuppression [40, 41].

As early diagnosis and treatment are key for optimal graft salvage, most patients undergo a series of pre-determined endoscopies and biopsies several times weekly during the immediate post-operative period. Clear histologic criteria have been established to aid in the diagnosis of ACR, as determined by the 8th International Small Bowel Transplantation Symposium in 2003, with the severity of ACR ranging from indeterminate to severe based on the degree of crypt injury, apoptosis, and architectural distortion [42].

Despite active interest in identifying means of non-invasively monitoring patients for ACR, no ideal molecules have yet been identified. While plasma citrulline and fecal calprotectin have both been studied as potential targets, these biomarkers remain unreliable. In particular, significant inter-patient variability has been reported in studies of calprotectin, while citrulline has been shown to be non-specific for ACR, as levels have been shown to be elevated in a multitude of inflammatory states [43, 44].

With regards to treatment, mild-moderate ACR is well-controlled with pulse steroids for 3–5 days and increasing the maintenance dose of tacrolimus. In contrast, patients with severe ACR generally require treatment with pulse steroids in addition to rATG [22].

Although not as common as ACR, chronic rejection (CR) is an emerging problem in intestinal transplantation, perhaps due to improvements in treatment of ACR and subsequent overall graft survival [19, 45]. Clinically observed as reduced absorptive function of the intestinal allograft leading to increased stoma output or diarrhea, CR is histologically characterized by arterial intimal hyperplasia leading to ischemia and fibrosis [46]. As with other solid organs, the management of CR remains limited to date and primarily focused on symptom management and re-transplantation when clinically required [47].

Infections

Affecting up to 91% of patients in one series, infection remains the single most common cause of morbidity and mortality for patients undergoing intestinal transplantation [48]. This is especially true for patients during the first year following transplantation, with a reported 90–100% risk of bacterial infection, 15–30% risk of cytomegalovirus (CMV) infection, and a 30–50% risk of fungal infection [49].

Viral infections including CMV, Epstein Barr virus (EBV), and adenovirus are particularly cumbersome to manage as they are difficult to prevent and, at times, difficult to diagnose given their clinical similarity to ACR. While most centers screen for and, if possible, avoid the use of CMV-positive organs in CMV-negative recipients, this is not always feasible given ubiquitous nature of CMV infection. To mitigate the infectious risks associated with the use of CMV-positive organs, prophylaxis and/or treatment with ganciclovir and CMV immune globulin (CytoGam) have become routinely used in many [50, 51].

Although the incidence of post-transplant lymphoproliferative disease (PTLD) may be declining due to enhanced screening techniques and protocols, EBV-associated PTLD remains the most common malignancy following ITx, occurring in approximately 13% of patients [52, 53]. Frequent manifestations include diarrhea, weight loss, and lymphadenopathy, while central nervous system involvement may be indicated by complaints of headache, seizures, nausea, or even coma. Diagnosis typically involves confirmatory EBV titers in addition to imaging such as MRI, CT, or positron emission tomography (PET) scans [19]. Treatment consists of both reducing maintenance immunosuppression and, in cases with CD20+ B cell predominant disease, treatment with rituximab [54].

Graft Versus Host Disease

Despite the large volume of lymphatic tissue transplanted as part of an intestinal graft, graft versus host disease (GVHD) is uncommon following ITx, occurring in less than 10% of patients [41]. Unlike GVHD following bone marrow transplantation, GVHD post ITx does not affect the allograft, but native stomach, small bowel, or colon may be involved. Typically causing a diffuse maculo-papular rash of the skin, GVHD may also affect the lungs and bone marrow, a clinical progression carrying significant morbidity and mortality [48, 55, 56]. Diagnosis is often confirmed via biopsy of the native rectum. Treatment typically consists of increased maintenance immunosuppression and pulse steroids.

Outcomes

Due to advancements in immunosuppression as well as the medical and surgical care of patients both pre- and post-transplant, outcomes following intestinal transplantation have improved drastically in recent decades [52]. Notably, per the last OPTN/SRTR report for 2015, the graft failure rate for patients of all ages undergoing ITx was 19.3 and 24.5% at 6-months and 1 year post transplant, 42.4% at 3 years, 54.8% at 5 years, and 66.2% at 10 years [38]. Graft failure rates following LITx are similar, with reported rates of 17.6, 27, 33.8, 48.7, and 50.9% at 6 months and 1, 3, 5, and 10 years, respectively [38]. The fact that combined liver–intestine grafts exhibit less graft failure at almost all time points is notable. This finding may be due in large part to the high incidence of observed rejection in isolated intestinal grafts, as well as the tolerogenic properties of liver-derived lymphocytes which are widely believed to confer a protective survival advantage to organs which are co-transplanted with liver allografts [41, 45, 57–59]. Amongst pediatric patients (<18 years) who underwent intestinal transplantation with or without simultaneous liver transplantation between 2008 and 2010, 1- and 5-year graft survival was 72.6 and 56.8% per the 2015 SRTR data [38]. In similar fashion, patient survival at 1- and 5-years among children was 88.1 and 77.4% following ITx and approximately 78 and 63% following LITx [38]. The Pittsburgh pediatric experience is similar, with nearly 5-year 80% patient survival for both ITx as well as LITx cohorts [60]. Although 15-year survival for all patients undergoing isolated and combined intestinal transplantation has been reported to be about 35%, this data should be viewed with caution given wide variations in medical management and immunosuppression over that same timeframe [31].

With regards to living-donor outcomes, long-term outcomes remain limited due to small numbers. Recently, Aroz et al. reported outcomes of 10 pediatric patients who underwent living-donor ITx and LITx for IF between 2002 and 2013 [18•]. Of these children, seven of 10 are alive with a functioning allograft and tolerating full enteral nutrition, with six of these patients having greater than 10 years of follow-up. Two patients experienced at least one episode of acute rejection, with one patient later developing chronic rejection requiring allograft explant. There were three patient deaths, due to PTLD, intraoperative death during re-transplantation, and chronic graft failure secondary to chronic rejection.

Conclusion

Intestinal transplantation, either in isolation or as part of a composite graft, has become an increasingly safe and effective means of treating patients with IF and complications secondary to chronic PN dependence. Long-term outcomes for patients with IF have drastically improved given advancements in our understanding of IF, intestinal rehabilitation, hepatoprotective PN strategies, and intestinal reconstructive options, making intestinal transplantation a treatment of last resort for most patients. Despite this, early evaluation and collaboration with a transplant center should be a top priority so that patients may be closely monitored and readily listed for transplantation should there be significant clinical changes.

Compliance with Ethical Guidelines

Conflict of interest Drs. Lee and Kim declare no conflicts of interest relevant to this manuscript.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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enteral autonomy was achieved in 43% of patients, while 13% remained dependent upon PN and 43% of patients died or were transplanted. On multivariate analysis, an underlying diagnosis of necrotizing enterocolitis [OR 95% CI: 2.42 (1.33, 4.47)], care at an intestinal failure center which was not associated with a transplant center [OR 2.73 (1.56, 4.78)], and the presence of an intact ileocecal valve [OR 2.80 (1.63, 4.83)] were all independently associated with achieving enteral autonomy.

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