Current Perspectives on Pediatric Intestinal Transplantation

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Irreversible intestinal failure in children is predominantly caused by surgical conditions such as volvulus, necrotizing enterocolitis, and gastroschisis. Functional intestinal failure from motility disorders such as intestinal pseudo-obstruction or enterocyte dysfunction with microvillus inclusion disease also may require intestine replacement. Approved indications for intestinal transplantation include liver dysfunction, loss of major venous access, frequent central line–related sepsis, and recurrent episodes of severe dehydration despite intravenous fluid management. Surgical options include transplantation of the isolated intestine, combined liver-intestine transplantation, or multivisceral transplantation of the stomach, duodenum, pancreas, and small bowel (with or without the liver). Immunosuppression for intestinal transplantation is based on tacrolimus therapy, often with induction immunosuppression using antilymphocyte antibodies (eg, antithymocyte antibody and alemtuzumab). Experience at centers of excellence demonstrates 1- and 5-year patient survival rates of 95% and 77%, respectively, with ongoing investigations focusing on lowering long-term causes of graft loss such as chronic rejection.

Introduction

Intestinal transplantation continues to demonstrate significant progress in early to intermediate patient and graft outcomes. This success has been the result of improved multidisciplinary patient care of the patient with intestinal failure as well as refined surgical techniques and post-transplantation care. This article discusses current data on procedures performed and outcome measures in pediatric intestinal transplantation, and reviews areas of recent advancement and ongoing focus.

Indications

Diseases associated with loss of intestinal function can be divided into surgical and nonsurgical etiologies [1]. Patients with surgical causes generally suffer from loss of bowel length after resection or from strictures and fistulas, as with Crohn's disease. In nonsurgical causes of intestinal failure, the anatomic length and gross morphology of the intestine are usually normal. Nonsurgical causes of intestinal failure include motility disorders (eg, intestinal pseudo-obstruction or Hirschsprung's disease) and absorptive problems (eg, microvillus inclusion disease). The indications for transplantation in the case experience at the University of Pittsburgh and Children's Hospital of Pittsburgh are listed in Table 1.

Parenteral nutrition (PN) is the standard of care for patients with intestinal failure who are unable to maintain a normal balance of nutrition, fluid, and electrolytes by use of the gastrointestinal tract alone. Management of intestinal failure is best accomplished with a multidisciplinary effort by gastroenterology, pediatric surgery, nutrition, and allied services to maximize the patient's opportunities for bowel rehabilitation [2,3•,4,5]. Improved long-term outcomes for 245 children managed with PN have been reported recently in single-center experiences [6–8]. Clearly, however, a group of patients persists who develop irreversible intestinal failure and require indefinite PN, with its attendant complications. Intestinal transplantation may be lifesaving in this group [9].

Decisions regarding the best transplantation options are primarily based on functional assessment of the status of the remaining intestine and of the liver [10]. In October 2000, the US Centers for Medicare and Medicaid Services [11] approved intestinal, combined liver/intestinal, and multivisceral transplantation at centers of excellence as standard of care for patients with irreversible intestinal failure who could no longer be maintained on PN because of 1) impending liver failure, as manifested by jaundice or elevated liver injury tests, clinical findings (splenomegaly, varices, coagulopathy),

Table 1. Disease indications for composite and isolated intestinal transplantation

Pediatric patients, %	Adult patients, %
Gastroschisis, 25%	Porto-mesenteric thrombosis, 35%
Volvulus, 24%	Crohn's disease, 17%
Necrotizing enterocolitis, 12%	Desmoid tumor/familial polyposis, 9%
Pseudo-obstruction, 10%	Other, 9%
Intestinal atresia, 9%	Pseudo-obstruction, 9%
Hirschsprung disease, 7%	Trauma, 7%
Microvillus inclusion disease, 5%	Volvulus, 6%
Other, 4%	Intestinal adhesions, 5%
Trauma, 2%	Radiation enteritis, 3%
Intestinal polyposis, 1%	
Tufting enteropathy, 1%	

history of stomal bleeding, or hepatic cirrhosis on biopsy; 2) loss of major venous access defined as more than two thromboses in the great vessels (subclavian, jugular, and femoral veins); 3) frequent central line–related sepsis consisting of more than two episodes of systemic sepsis per year, or one episode of line-related fungemia associated with septic shock or acute respiratory distress syndrome; or 4) recurrent episodes of severe dehydration despite intravenous fluid management.

Replacement of the liver along with the intestine is based on biochemical dysfunction (hyperbilirubinemia, transaminase abnormalities, hypoalbuminemia, thrombocytopenia, or coagulopathy), presence of bridging fibrosis or cirrhosis on liver biopsy, or the presence of portal hypertension. Hypercoagulable patients deficient in protein S, protein C, and antithrombin III may develop diffuse thromboses within the splanchnic system and require multivisceral transplantation.

The Transplantation Operation

Abdominal visceral procurement

Donor selection and the satisfactory procurement of intestine-containing allografts is critical to maximizing graft function and, in the case of the isolated intestinal transplantation, can be completed without sacrificing other abdominal viscera [12,13]. Improving donor utilization is also critical to decreasing wait-list mortality. Traditionally, donors who suffered cardiopulmonary arrest were considered poor candidates for intestine recovery. Recently, however, Matsumoto et al. [14•] reported no significant difference in survival, rejection, length of stay, or time to enteral independence in 12 recipients of organs from donors who received cardiopulmonary resuscitation for a mean duration of 19.3 ± 12.7 minutes (range 1–52) compared with 55 recipients of organs from donors who did not. Patient and graft survival at 1 year was 79% in the former group compared with 82% in the latter group.

Neonatal and infant donors are a potentially underutilized resource. Of note in recent analyses [15••,16], the death rate in the first year after transplantation for children receiving a graft from an infant donor, expressed in 1000 patient years at risk, fell to 248 in 2006 compared with 379 in 2004 and 364 in 2005, highlighting the need for aggressive consideration of even the youngest donors.

An important consideration is proper size matching between recipient and donor. Significant reduction of abdominal capacity because of prior bowel resection is common in these patients and is of particular importance in the very young, for whom size-matched donors are infrequent. Allograft reduction and efforts to provide increased abdominal capacity, whether via abdominal wall transplantation or delayed closure measures, have been performed to expand the donor pool [17]. The lifesaving nature of these allografts must be balanced with the potential complications of the reduced allograft, such as less optimal bowel adaptation, ongoing intravenous fluid dependency, and need for continued line access. Even with size-reduced organs, wound closure poses significant clinical problems and requires thoughtful management [18].

Recipient operations

Obtaining sufficient vascular access, especially when the liver requires transplantation, is critical to successful intraoperative and postoperative management and can be challenging in patients with significant loss of venous access. The recipient operation consists of removal of the failed organs after exposure of the vascular anatomy, followed by allograft implantation, as described below.

Isolated small bowel

In cases of surgical short gut, the recipient's diseased small intestine is removed and the superior mesenteric artery (SMA) of the donor bowel is sewn to the infrarenal aorta (or the native SMA), and the donor superior mesenteric vein is anastomosed to the recipient superior mesenteric vein or inferior vena cava (Fig. 1*A*). The anastomoses may be facilitated by the use of interposition arterial and venous grafts. Intestinal continuity is completed with proximal and distal gastrointestinal anastomoses, and access to the ileum for endoscopic examination is provided by a temporary chimney ileostomy, except in the case of a permanent end-ileostomy.

Utility of the colon

Early experience with the use of a donor colon as part of the allograft transplantation was accompanied by an increased incidence of infectious complications. More recently, the colon has been transplanted without an increase in morbidity and mortality (Fig. 1*A*) [19]. The

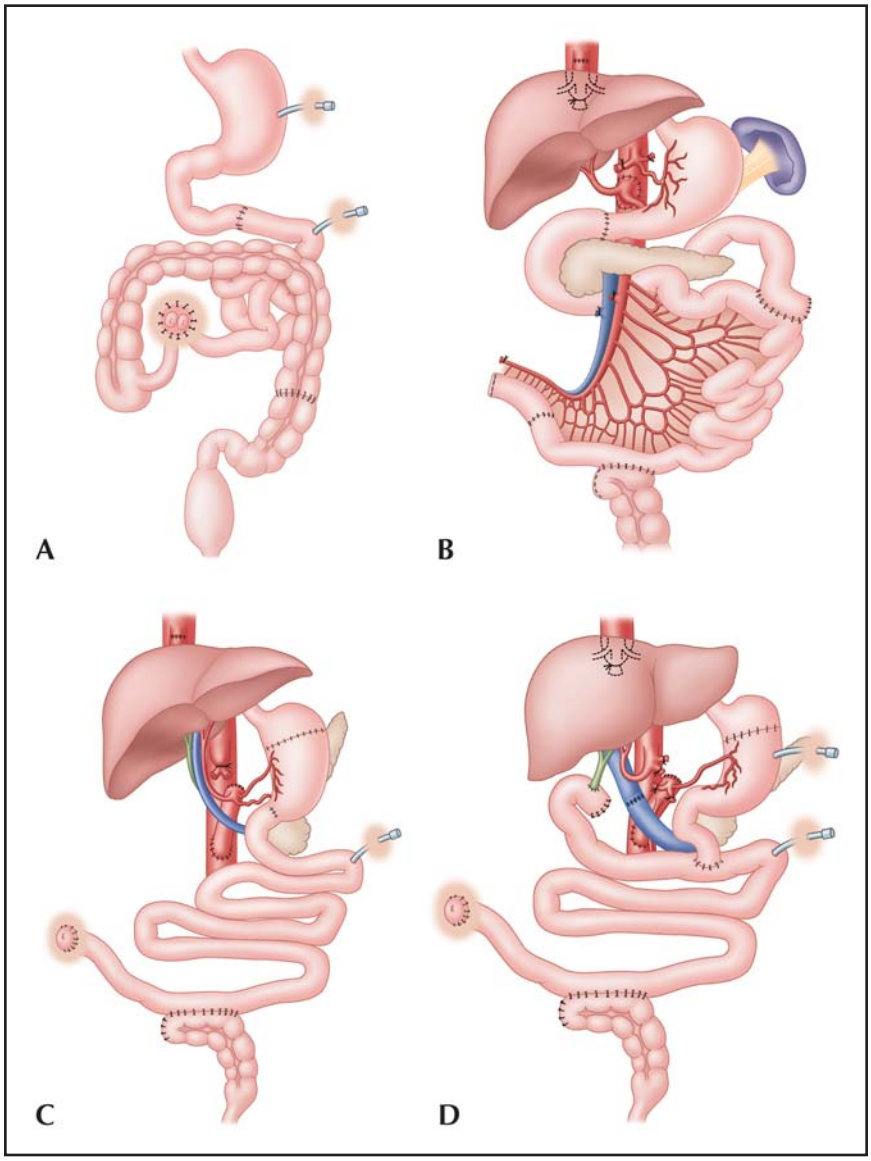

Figure 1. A, An isolated small bowel with colon graft; the loop ileal chimney allows easy access to bowel mucosa. **B,** Composite liver and intestinal graft with preservation of the duodenum in continuity with the graft jejunum and hepatobiliary system. **C** and **D**, Diagrams of multivisceral donor organs: **C,** complete; **D,** modified multivisceral.

most important indication for colon transplantation is anticipated need for increased fluid resorption by the successfully transplanted colon, particularly in patients with secretory disorders or who otherwise would require a permanent ileostomy.

Liver and small bowel

The diseased liver is removed with the retrohepatic vena cava preserved in situ ("piggyback"), and a permanent portal-caval shunt draining the native stomach and pancreas is performed (Fig. 1*B*). Before implantation of the allograft, the double arterial stem of the celiac and superior mesenteric arteries (using the Carrel patch technique) is connected to the infrarenal aorta using a donor aortic conduit homograft. A proximal jejunojejunostomy, ileocolostomy, and a temporary distal ileostomy complete the operation. The allograft duodenum remains in continuity with the allograft biliary system [13].

Multivisceral transplantation

Significant dysmotility in the native stomach, portal venous thrombosis, or major trauma or dysfunction of the pancreatoduodenal complex are the main indications for replacement of the stomach. After removal of the native liver, distal stomach, duodenum, pancreas, and intestine, the retroperitoneal aorta is exposed and the multivisceral graft connected to its vascular inflow and outflow. With a full multivisceral transplant (liver included), the suprahepatic venous attachment is completed initially, followed by the aorto-aortic anastomosis (Fig. 1*C*). No portal vein anastomosis is required in this procedure, because the recipient's portal vein and its inflow native organs (gastrointestinal tract, pancreas, and liver) are removed with the enterectomy. Patients with a normal native liver receive a modified multivisceral procedure in which allograft portal venous return is directed into the recipient's native portal vein, preserving the native liver (Fig. 1*D*). A gastrogastric anastomosis, coloenteric anastomosis, and a

chimney ileostomy are routinely performed. A pyloroplasty is also necessary, due to vagal denervation, to avoid gastric outlet obstruction. In all types of intestinal recipients, the ileostomy is primarily placed to allow for ease of allograft monitoring via ileoscopy and ileal allograft biopsies. "Take-down" of the ileostomy can be performed once oral nutrition is consistently adequate and a stable immunosuppressant regimen has been achieved, minimizing the need for frequent endoscopic surveillance.

Post-Transplantation Management

Immunosuppression

The immunosuppression regimens used throughout the world continue to evolve [20]. Primary induction therapy with either rabbit antithymocyte globulin (rATG) (Thymoglobulin, Genzyme Corp., Cambridge, MA) or alemtuzumab (Campath-1H, Genzyme Corp., Cambridge, MA) is increasingly common [21–24].

Rejection is treated with optimization of tacrolimus levels, supplemental corticosteroids, and monoclonal or polyclonal antibody if necessary. Additional or alternative agents occasionally have been used, including azathioprine, rapamycin, and mycophenolate mofetil.

Immunosuppression protocols and tolerance

Considerable progress has been made in using immunosuppression strategies to improve early graft outcomes while minimizing toxicity. Although drug minimization (steroid-free, spaced monotherapy) is successfully achieved in some patients, the goal of complete immunosuppression avoidance in the intestinal recipient has not been achieved. Considerable work is necessary to identify those in whom immunologic activity may allow for drug weaning and, conversely, others at risk of rejection [25,26,27••]. Investigations into the importance of preformed antibody and treatment of the sensitized recipient are ongoing [28–30]. Anti-donor antibody measurement may assist in determining risk of rejection and may be useful in the clinical management of the patient following intestinal transplantation [26].

Postoperative care

The main focus of post-transplant care is the management of rejection and infection. For a comprehensive discussion of postoperative care of the intestinal transplant patient, the reader is referred to an excellent review of the topic [31].

Gastrointestinal function and assessment

The normal intestine is pink and nonedematous and occasionally demonstrates contractions. Changes in the ileal stoma postoperatively should be promptly investigated, and vascular, technical (eg, prolapse), or immunologic causes ruled out. Dramatic and rapid changes may be seen in recipients of a positive tissue typing cross match, especially B cell, which may be associated with an increased risk of a humoral (antibody-mediated) rejection.

Routine endoscopic surveillance is used to assess graft integrity and to diagnose intestinal rejection. Normal stomal output is 40 to 60 mL/kg/d. No reliable serum tests exist for monitoring the function of intestinal grafts. Data on prospective markers (eg, citrulline) are inconclusive, as are the data on fecal calprotectin [32–36].

Management of complications

Graft rejection

Clinically, intestinal allograft rejection may be asymptomatic or may present with fever, abdominal pain, distention, nausea, vomiting, and a sudden increase or decrease in stomal output. The stoma may appear normal or may lose its normal velvety appearance and become friable or ulcerated. Histologically, rejection is graded by the degree of epithelial damage [37]. In mild rejection, epithelial cell apoptosis leads to epithelial cell loss within the deep crypts. In moderate rejection, crypt damage is more severe with focal crypt loss. Severe rejection may lead to denuded mucosa. Regeneration occurs by re-epithelialization over the surface of a lamina propria devoid of crypts. In most cases, mild graft rejection responds to intravenous methylprednisolone, with optimization of serum tacrolimus levels to 15 ng/mL. Antibody therapy is used when rejection has progressed despite a steroid pulse, or as the initial therapeutic agent in cases of severe mucosal injury and crypt damage.

Chronic rejection is observed in 10% to 15% of patients, and appears more common in recipients of isolated intestinal allografts. The presentation may include weight loss, chronic diarrhea, intermittent fever, distal ileal obstruction, or gastrointestinal bleeding. Histologically, villous blunting, focal ulcerations, epithelial metaplasia, and scant cellular infiltrates are present on endoscopic mucosal biopsies. Full-thickness intestinal biopsies show obliterative thickening of intestinal arterioles.

Outcomes

World experience [20], US data [15••,16], and single-center experiences [22,38] are briefly summarized here. The International Transplant Registry [20] reports that about 100 to 120 pediatric intestine-containing transplants currently are performed annually. In an analysis of recent experience, 503 children received 520 grafts (192 isolated intestinal grafts, 210 liver and small bowel grafts, and 118 multivisceral grafts) between 2002 and 2007 [20]. Being at home rather than hospitalized when called for transplant, use of induction immunosuppression, and transplantation at a high-volume center (> 10 cases experience) are associated with better short- and intermediate-term patient and graft survival.

In the United States in 2007, 198 adults and children received an intestinal transplant, the most ever in 1 year

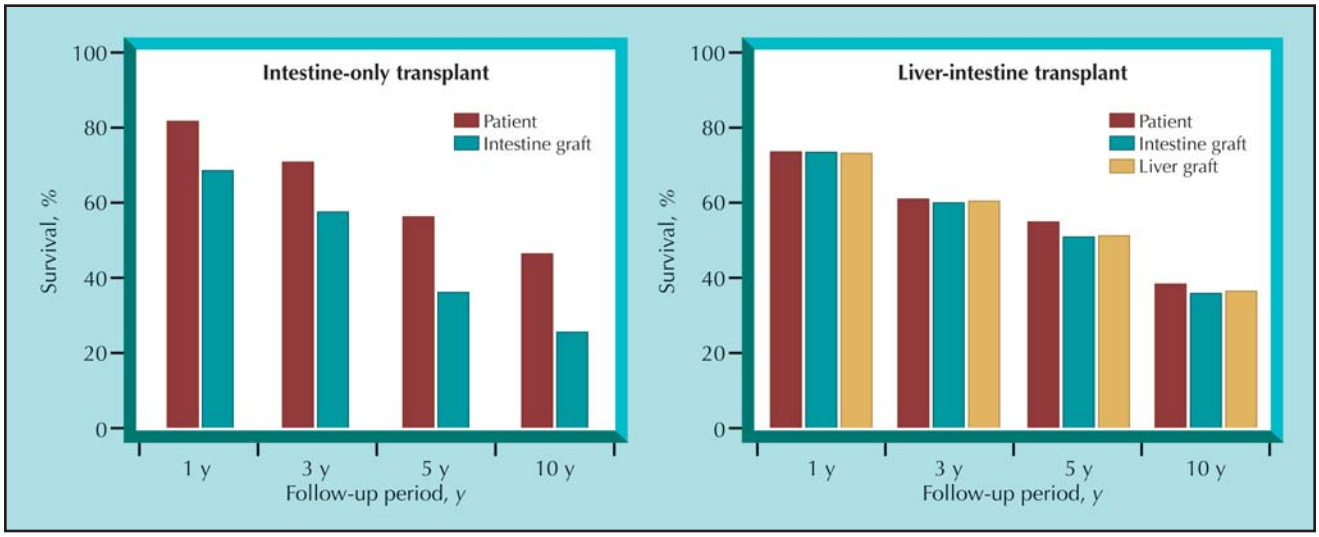

Figure 2. Patient and graft survival rates in the United States by intestinal graft type.

[15••]. Children ages 1 to 5 composed 28% of the total group. The majority received liver-intestine allografts, highlighting the ongoing need for proper timing of referral to optimize the opportunity for the intestine's adaptation, and thus to lower the number of patients who ultimately develop PN-associated liver disease that requires liver replacement. Patient and graft survival at 1, 3, 5, and 10 years are shown in Figure 2.

In the experience at the University of Pittsburgh, 457 patients received 507 total intestinal grafts from May 1990 through December 31, 2008. Of those, 199 (44%) were children with a mean age of 5.1 ± 5.3 years (range 0.4–21.3) and a mean weight of 18.7 ± 14.8 kg (range 5.1–74), who received 218 total allografts. Organ type was isolated intestine in 71 (36%), liver-intestine in 98 (49%), full multivisceral in 25 (13%), and modified multivisceral in five (2%). Current mean follow-up is 55.4 months (median 42.5 months, range 1–225). Immunosuppression was based on tacrolimus and steroids from 1990 to 1998 (n = 50), with additive cyclophosphamide from 1995 to 1997 (n = 16) or daclizumab (Zenapax, Roche Group, Nutley, NJ) from 1998 to 2001 (n = 23). Since 2002, immunosuppression was based on preconditioning and induction with 5 mg/kg intravenous rATG (n = 100) or alemtuzumab (n = 10). Currently, 93% of survivors are completely free from total PN, and 1-, 3-, and 5-year patient survival rates are 95%, 84%, and 77%, with corresponding graft survival rates of 88%, 74%, and 58%, respectively, which compare favorably with the multisite data in Figure 2.

Acute rejection risk has diminished to 30% with alemtuzumab induction and 62% with rATG induction, from a historical rate of 80%. Concurrent with the advent of improved infectious disease monitoring, the incidence of cytomegalovirus (CMV) and Epstein-Barr virus disease or post-transplant lymphoproliferative disorder (PTLD) similarly decreased from 22% to 14% for CMV and from 38% to 11% for PTLD.

Critical and Controversial Issues in Intestinal Transplantation

Organ availability and allocation

Analysis of outcomes of patients on the wait list for an intestinal transplantation in 2006 revealed that 54% had received a transplant within 1 year, 17% had died within a year of listing, and 21% remained on the list; of the 8% removed from the list, 6% were removed for worsening or other conditions and only 2% were removed for improved condition [15••,16]. Of the 222 candidates on the intestine wait list in 2007, 63% were children under the age of 5. Children younger than 1 year of age and between the ages of 1 and 5 years waited a median time of 321 and 241 days, respectively, for transplantation. Although overall time to transplant has improved for intestinal transplantation candidates, wait-list mortality remains the highest for intestinal transplantation among all solid organ transplant candidates. Further, the death rate in pediatric patients awaiting liver and intestinal transplantation is disproportionately higher than in those requiring intestinal alone, especially in the very small patient (< 1 year), for whom obtaining appropriate size-matched donor organs is difficult [39,40]. Results of attempts to increase the Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease (MELD/PELD) score so that these patients can be transplanted earlier are being assessed.

Live donor intestinal and combined liver/intestinal allografts

Some early attempts at intestinal transplantation involved living donors, but results were suboptimal with no long-term survivors and many suffering from chronic rejection.

Renewed attempts at this procedure have been more successful, although long-term results are still needed [41–43]. Whether live donor isolated intestinal transplantation is needed is the subject of ongoing debate, especially because optimizing use of deceased donor allografts should alleviate the donor shortage, except perhaps in the very young. A promising approach to consider is the combined liver/intestinal live donor transplant, particularly for the small infant, which may overcome a lack in the appropriate size-matched donor pool [40].

Liver-alone transplantation in patients with intestinal failure

The very young infant with gut dysfunction is more susceptible to PN-associated liver failure. These livers may fail before the patient has had time for intestinal adaptation to be maximized. It is believed that some patients, if given enough time, would undergo enough further intestinal adaptation to avoid the need for intestinal transplantation. Criteria for patient selection for liver-alone transplantation reported by Botha et al. [44] included history of at least 50% enteral tolerance, age less than 2 years, and no underlying intestinal absorptive disorder. In this series, bowel length ranged from 25 to 100 cm, and 23 children underwent 28 isolated liver transplants. Patient and graft survival rates were 82% and 75% at 1 year and 72% and 60% at 5 years. Of the 17 surviving patients, 14 achieved independence from PN.

Chronic rejection and retransplantation

Patient and graft survival rates for intestinal and multivisceral transplantation continue to improve, with results in some experienced centers nearing that of liver transplantation. However, long-term outcomes, particularly with transplant of the isolated intestine, are of concern, with chronic rejection a significant cause of delayed graft loss [45]. Retransplantation of the intestine was traditionally associated with poor results [20]. Recent data demonstrate that more acceptable long-term results can be obtained: in one report, 14 (8.1%) of 172 children undergoing intestinal transplantation underwent a repeat intestinal transplantation [46]. Although perioperative management is complex, a 71% patient survival rate was reported with a mean follow-up of more than 4 years. Currently, median follow-up in this cohort is 45 months (range 22–140).

Additional areas of investigation

Other areas of investigation of considerable importance to the clinician caring for intestinal transplant recipients include assessment of outcomes (neurodevelopmental, quality of life, growth, and nutrition) [47–50].

Conclusions

At the end of 2006, more than 500 US recipients enjoyed a functioning intestinal transplant [15••]. Of these, 44% were transplanted when they were less than 5 years of age. The increasing number of patients with a successful intestinal transplant highlights the need for progress in addressing long-term concerns such as chronic rejection and late graft loss. Developing more widely shared consensus for proper timing and referral of the patient with intestinal failure, improving efforts at intestinal rehabilitation, and reducing wait-list mortality are critical. Continued advancement in the field of intestinal and multivisceral transplantation requires an ongoing, concerted effort and dedication from a multidisciplinary team of health care professionals so that this extremely challenging group of patients can receive optimal care with the best chance of successful long-term outcome.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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