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Intestinal transplantation in children: current status

Andrea Martinez Rivera[1,2] · Paul W. Wales[1,3]

Abstract Intestinal transplantation (IT) is the least common form of organ transplantation; however, it has shown exceptional growth and improvement in graft survival rates over the past two decades mainly due to better outcomes achieved during the first year of transplantation (76 % at 1 year), due to improvement in surgical techniques and the development of better immunosupressive therapies as we understand more about the relationship between the recipient and host immune system. There are still ongoing issues with chronic rejection and long-term survival. Intestinal transplantation is still an acceptable therapy for patients with intestinal failure (IF), but it is generally reserved for patients who develop severe and life-threatening complications despite standard therapies, or those who are not able to maintain a good quality of life. The purpose of this review is to describe the current status, indications, outcomes and advances in the field of intestinal transplantation.

Keywords Intestinal Failure (IF) · Intestinal Transplantation (IT) · Intestinal Rehabilitation Programs (IRP) · Intestinal Transplant Registry (ITR) · Parenteral Nutrition (PN) · Central Venous Catheter (CVC)

✉ Paul W. Wales
  paul.wales@sickkids.ca

1   Group for the Improvement of Intestinal Failure and Treatment (GIFT), The Hospital for Sick Children, University of Toronto, Toronto, Canada

2   Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, University of Toronto, Toronto, Canada

3   Division of General and Thoracic Surgery, The Hospital for Sick Children, University of Toronto, Toronto, Canada

Introduction

Intestinal transplantation (IT) is the least common form of organ transplantation; however, it has shown exceptional growth and improvement in graft survival rates over the past two decades mainly due to better outcomes achieved during the first year of transplantation (76 % at 1 year), although rates of graft loss beyond 1 year have not improved [1]. Historically, intestine has been considered a non-transplantable organ due to large amount of lymphoid tissue included in the graft. With the development of better immunosuppressive management (cyclosporine in 1978 and tacrolimus in 1989) and enhancements in our understanding of the relationship between recipient and host immune systems [2], as well as improvement in surgical techniques and improved methods to prevent and monitor infections, the survival rate has improved. There are still ongoing issues with chronic rejection mainly due to the lack of knowledge and understanding of donor-specific antibody (DSA) development or early non-invasive detection of acute rejection [3].

IT remains an acceptable therapy for patients with intestinal failure (IF), but it is generally reserved for patients who develop severe and life-threatening complications despite standard therapies, or those who are not able to maintain a good quality of life. Intestinal failure is defined as the reduction of functional gut mass below the minimal amount necessary for digestion and absorption of adequate nutrients and fluids for survival and growth. IF occurs secondary to either anatomical or functional loss of a portion of the intestine. The leading cause of pediatric IF is short bowel syndrome (SBS) followed by dysmotility syndromes and mucosal enteropathies [4]. Approximately 15 % of children with intestinal failure develop life-threatening complications despite optimal medical and

surgical treatment [5]; however, IF prognosis has improved dramatically in the past two decades through the development of new medical and surgical therapies and the introduction of multidisciplinary intestinal rehabilitation programs (IRP) with an overall improvement on patient survival [6]. Mortality while waiting for transplantation is higher compared to other solid organ transplantation; therefore, early referral for assessment is critical to optimize outcome [7]. The purpose of this review is to describe the current status, indications, outcomes and advances in the field of intestinal transplantation.

Current status

The intestinal transplant registry (ITR) has gathered information on the outcomes of small bowel transplantation biannually since 1985 [8, 9]. The ITR database currently includes patient information from 82 contributing centers that provided data on 2887 transplants, performed in 2699 patients, who were transplanted on or before February 2, 2013. There are mainly ten programs contributing the largest number of patients to the latest report: Clarian Transplant Center (Indianapolis), Georgetown University Hospital (Washington, DC), Mount Sinai Hospital (New York), Hospital for Sick Children (Toronto), UCLA (Los Angeles), University of Miami (Miami), University of Nebraska (Omaha), University of Paris (Paris) and UPMC (Pittsburgh). The busiest programs are still located in North America and Europe, however the greatest percentage of recent activity has occurred in centers located in South America. The latest report showed that there had been a steady growth in the overall intestinal transplant volumes over the past 3 decades, until 2008 when transplant activity began to decline (Fig. 1) [1]. This decline may be related to the introduction of multidisciplinary intestinal rehabilitation programs (IRP) to treat IF and new medical therapies, including ethanol locks to reduce catheter related sepsis, novel lipid management strategies, and surgical advances in autologous bowel reconstruction [4, 10–21].

Indications

The major goals of IT are discontinuation of parenteral nutrition (PN) and oral autonomy. The indications for IT in the pediatric population have not changed overtime (Fig. 2). The most common cause of IF failure in children is short bowel syndrome (SBS) (63 %),that arises typically from neonatal conditions such as, gastroschisis, intestinal volvulus, intestinal atresia and necrotizing enterocolitis. IF is also caused by motility disorders (18 %), mucosal enteropathies (8 %) and re-transplantation (8 %) (Table 1).
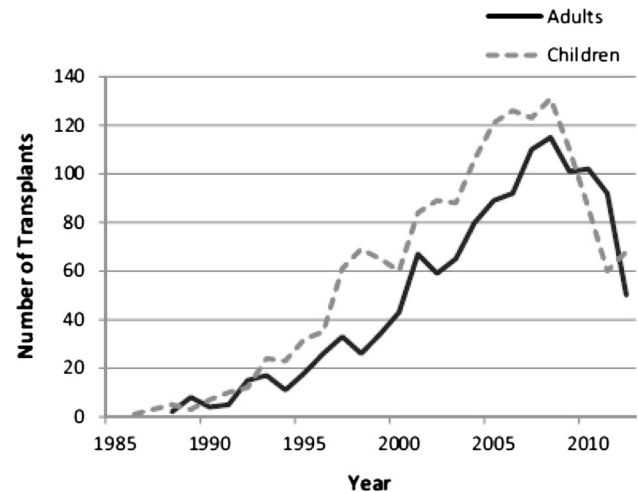

Fig. 1 Trends in case volumes over time. Although volumes have increased over time, clinical activity has declined since 2008
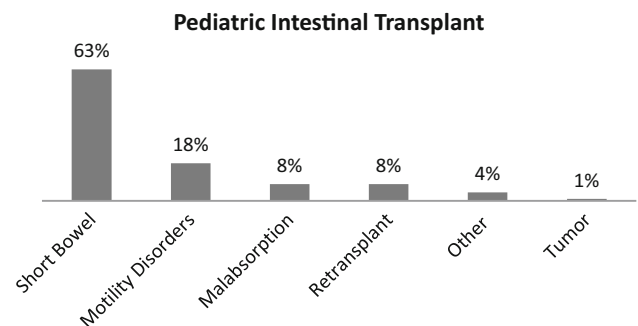

Fig. 2 Indications for intestinal transplantation in children

The official indications have not changed overtime as reported by the intestinal transplant registry in 2015. Approximately 10 % of children with IF will need either isolated IT or IT associated with other organs (liver/multivisceral) [7].

IT has been reserved for patients who develop severe and life threatening complications despite standard therapies or those who are not able to maintain a good quality of life. The current listing indications used for intestinal transplantation were developed by expert consensus and published in 2001 by Kauffman et al. [22]. They were subsequently adopted by The American Society of Transplantation and include:

1. Progressive intestinal failure associated liver disease with plasma bilirubin >3–6 mg/dl and signs of portal hypertension, or synthetic liver dysfunction with coagulopathy.
2. Recurrent life threatening episodes of sepsis resulting in multi-organ failure, metastatic infectious foci or acquisition of flora with limited antibiotic sensitivities.

Table 1 Causes of intestinal failure in children

Short bowel syndrome	Congenital
	Surgical
	Necrotizing enterocolitis
	Malrotation with midgut volvulus
	Gastroschisis
	Intestinal atresia
	Inflammatory bowel disease
	Trauma
Motility disorders	Long segment Hirschsprung disease
	Intestinal pseudo-obstruction
Enteropathies	Neonatal diarrheas
	Microvillious inclusion disease
	Tufting enteropathy
	Sodium channel diarrhea
	Autoimmune enteropathy
Other	Tumors
	Familial polyposis
	Inflammatory pseudotumor
	Ischemia

3. Loss of more than 50 % of the standard central venous access sites.
4. Small bowel length of <25 cm without ileo-cecal valve.
5. Congenital intractable mucosal disorders such as microvillious inclusion disease or tufting enteropathy, which usually leads to early death in infancy.
6. Intestinal failure with morbidity and poor quality of life.

Traditionally, there has been high incidence of mortality in patients referred late for transplant assessment, with an overall mortality of children in the US waiting for an intestine graft threefold higher compared to liver transplant candidates. Waitlist mortality reaches 251 deaths/1000 patient-years on the wait list. Moreover, post transplant survival rates for patients who are at home while awaiting transplantation is 15 % higher than those who undergo transplantation while admitted to hospital [23]. Therefore, early referral for transplant assessment is critical to decrease the mortality before and after transplant. These criteria are based on IF clinical outcomes experienced 20 years ago.

Current clinical outcomes of pediatric patients with IF have improved significantly; therefore, the existing indications for bowel transplantation may no longer apply. In a recent single center study published by Burghardt et al. in 2015, the 2001 criteria (advanced cholestasis, loss of >50 % central venous catheter (CVC) sites, 2 sepsis/year, ultrashort bowel) were compared in children with intestinal failure in the old era [1998–2005] ($n = 99$) and current era [2006–2012] ($n = 91$) to predict the need for IT using sensitivity, specificity, negative and positive predictive value (NPV and PPV). Two 2001 criteria demonstrated poor predictive value in contemporary patients—advanced cholestasis (PPV 64 % old vs. 40 % current era; sensitivity 84 vs. 65 %, respectively) and ultrashort bowel (PPV 100 % old vs. 9 % current era; sensitivity 10 vs. 4 %, respectively). Three newly proposed criteria had high predictive value: >2 ICU admissions ($p = 0.0001$, OR 23.6, 95 % CI 2.7–209.8), persistent bilirubin >75 μmol/L despite lipid management strategies ($p = 0.0005$, OR 24.0, 95 % CI 3.2–177.4), and loss of >3 CVC sites ($p = 0.0003$, OR 33.3, 95 % CI 18.8–54.0). There was 98 % probability of needing IT when two of these new criteria were present (Table 2). These findings suggest it is time to revisit and revise the listing criteria for IT to reflect the changes in the natural history of pediatric intestinal failure that have occurred as a result of modern therapies [24].

Table 2 Proposed revised intestinal transplant criteria

Proposed intestinal transplant criteria	PPV	NPV	Sensitivity	Specificity
Panel A				
≥2 admissions to ICU	86	80	26	98
Loss of ≥3 CVC sites	100	78	17	100
Persistent elevation of conjugated bilirubin (≥75 μmol/L) following 6 weeks of lipid strategies	75	89	67	92

Proposed intestinal transplant criteria	Odds ratio	95 % CI	*p* value
Panel B			
≥2 admissions to ICU	23.6	2.7–209.8	0.0001
Loss of ≥3 CVC sites	33.3	18.8–54.0	0.0003
Persistent elevation of conjugated bilirubin (≥75 μmol/L) following 6 weeks of lipid strategies	24.0	3.2–302.7	0.0003

Panel A: Sensitivity, specificity, positive predictive value, negative predictive value

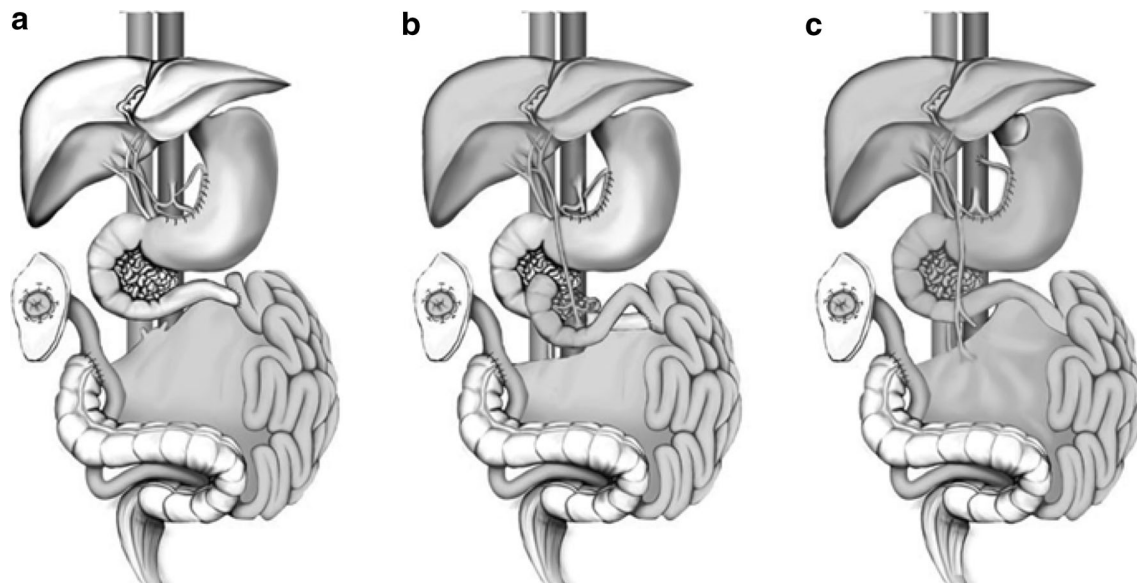Panel B: Chi-squared test and odds ratio

Fig. 3 Types of Intestinal transplantation. **a** Isolated intestinal transplant. **b** Combined liver-intestinal graft, which also contains in continuity, the donor duodenum and pancreas. **c** Multivisceral transplant, where the donor organs include liver, stomach, duodenum, pancreas, and small bowel

Nomenclature and types of grafts

The nomenclature to describe the various surgical techniques has not been consistent. In 2007, experts from major transplant programs met at the International Small Bowel Transplant Symposium in Los Angeles, CA. The consensus decision was to abandon the term multi-visceral transplantation. A more descriptive nomenclature was proposed. The new description was categorized based on whether or not the liver was included with the graft. The first category would represent the typical combined liver, small bowel and pancreas transplant. Modifiers to this operation would then reflect whether the transplant was performed with or without evisceration of the recipient foregut. The term isolated small bowel transplant remained as is and it may also include the stomach and the colon [25] (Fig. 3).

Isolated intestinal transplantation

The first and most universally agreed upon type of intestinal allograft is the isolated intestine. It is indicated in patients with irreversible IF without any significant liver disease. The isolated small bowel graft consists of the entire jejunum and ileum. The arterial inflow is supplied by the superior mesenteric artery and the superior mesenteric vein drains the isolated small bowel graft. In the small bowel allograft recipient, gastrointestinal continuity is re-established by anastomosis of the proximal native and donor jejunum and the distal bowel is brought out as a Bishop-Koop or loop ileostomy with or without anastomosis to the remnant native colon (Fig. 3) [26]. Isolated
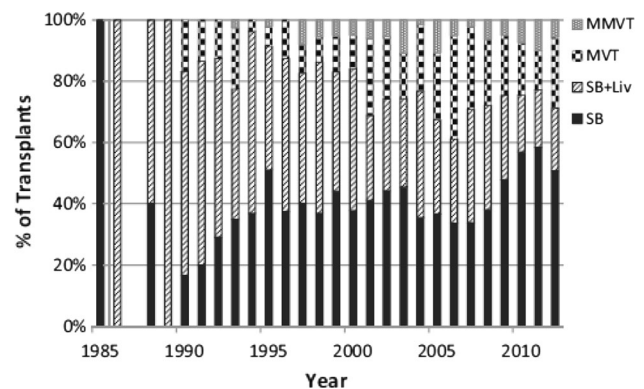

Fig. 4 This figure shows changes in the proportion of different types of intestine transplants over time. The proportion of cases with a concurrent liver component has steadily decreased ($p < 0.001$)

intestinal transplant is preferred surgical option due to shorter waiting time and the graft can be removed if necessary without compromising other organs. There has been a significant trend toward IT without a liver component (Fig. 4) [1]. Traditionally, this option has been considered in patients with a non-adaptable diagnosis such as ultra-short bowel syndrome, or mucosal enteropathies such as tufting enteropathy or microvillus inclusion disease.

Liver-intestine transplantation

This type of transplant is indicated for patients who suffer severe intestinal failure associated liver disease (IFALD) resulting in liver failure. In addition, they suffer intestinal failure and their remnant intestine has not demonstrated

adequate ability to adapt and be independent of PN support. Typically, enteral calorie tolerance of <50 % at time of transplant assessment would suggest listing for a combined graft. Patients with tolerance of >50 % of their calories enterally at the time of development of liver failure are potential candidates for isolated liver transplantation. The first combined liver-intestine transplant was described in 1990 by Grant et al. [27]. In this type of transplant, the inclusion of liver/duodenum/pancreas is a way of preserving the hepatic hilus and biliary tree; therefore, there is no need for biliary reconstructive procedures, decreasing the risks for donor-related vascular or biliary complications [28] (Fig. 3). The proximal bowel is anastomosed end to end with recipient native jejunum at the Ligament of Treitz, and the distal bowel is brought out as an end ileostomy or anastomosed end to end with the recipient bowel, with creation of a proximal diverting loop ileosotomy. Alternatively, the liver and intestine can be transplanted as individual organs, without the pancreas graft, which has the advantage that if the intestine allograft should develop severe rejection, it could potentially be removed without requiring re-transplantation of the liver [29].

Multivisceral transplant

This type of transplant is indicated for patients with severe pseudobstruction, Hirschprunǵs disease, motility disorders, localized non-metastazing tumors amongst other pathologies. It refers to the inclusion of other abdominal organs in continuity with intestine and stomach. These organs can include duodenum, colon, pancreas, spleen, kidney and if it also includes liver it is considered full multivisceral, if it does not include liver, then it is considered a modified multivisceral (Fig. 3).

The practice of colon inclusion in intestinal transplantation has evolved significantly over the past two decades, increasing from a rate of only 4 % in 2000 to a rate of 30 % in 2012. Early series had suggested that inclusion of the colon might increase the risk for infection; however, current clinical evidence supports the efficacy of selective and cautious use of the colon in intestinal transplantation as it is considered to carry a physiologic advantage by enhancing water absorption, residue breakdown, and storage as well as improving quality-of-life [30, 31].

Post operative management and short term complications

The early postoperative course is very challenging as it is affected by multiple factors including donor and recipient characteristics, status of the patient pre-transplant, type of transplant performed, and ischemia–reperfusion injury.

Nutritional management

It is the ultimate goal of IT to achieve enteral nutrition and wean PN. There are no guidelines on how and when to start enteral nutrition, but the general consensus based on a survey conducted at major transplant centers, is to start enteral feeds within 3–7 days once the surgical ileus has resolved [32]. Early introduction of feeds is important to stimulate gut hormones, so the general rule is to initiate low volume feeds, reduced in fat and low in osmolality, and slowly increase volume until full feeds are reached. There is then a transition to bolus feeds. Formula preference, including polymeric or elemental feeds, varies between centers. Due to manipulation of lymphatics during the surgery, it is suggested to avoid long chain triglycerides until 4–6 weeks. As oral aversion is common in many of these patients, almost 45 % of patients depend on enteral tube feeding for nutritional support for the first 2 years after transplantation [33]. If a patient does not have oral aversion, the diet should consist of low fat, low simple carbohydrates and low osmolality. Most children achieve normal carbohydrate and protein absorption within 3 months after transplantation. Micronutrient optimization including zinc, iron and copper is required after IT [34]. Weight gain and vertical growth is achieved within the first 6–12 months.

Acute rejection

The intestine is a highly immunogenic organ. Eighty percent of immune cells normally reside in gut and they are re-populated with recipient cells after transplantation; however, the genotype of the epithelium remains largely that of the donor, making the organ highly chimeric and immunogenic [35], with a higher likelihood of both acute and chronic rejection. Other than strict electrolyte and fluid management to maintain optimal organ perfusion in the immediate postoperative period, the main concern in the early postoperative course is the development of acute cellular rejection (ACR), which is a cellular and humoral immune-mediated allograft injury, that can occur in up to 50 % of patients and more frequently during the first 90 days post transplantation. Clinically, it can manifest in multiple ways including high stoma output, bloody diarrhea, fever and abdominal pain, amongst other symptoms and early recognition and treatment are crucial to ensure patient and graft survival. The exact mechanism of rejection is not yet well understood; however, there have been advances in the understanding of gut immunology during rejection, allowing better, targeted immunosuppression therapy. A recent study by Ningappa et al., demonstrated that among 107 differentially expressed genes, three B cell lineage-specific genes, CCR10, STAP1, and IGLL1, were

Table 3 Pathologic criteria for acute cellular rejection

No evidence of ACR—Grade 0	The tissue from the bowel allograft demonstrates unremarkable histological changes that are essentially similar to normal native bowel or pathologic changes are separate from ACR
Indeterminate ACR	Minor amount of epithelial cell injury or destruction is present, principally manifested in the crypts
	Increased crypt epithelial apoptosis but <6 apoptotic bodies/10 crypt cross section
Mild ACR—Grade 1	Crypt injury
	Increased mitotic activity, and/or crypt destruction with apoptosis (>6 apoptotic bodies/10 crypt cross sections)
	Villus blunting and architectural distortion
Moderate ACR—Grade 2	Focal or diffuse crypt injury and destruction
	>6 apoptotic bodies as described for/10 crypt cross sections, with foci of confluent apoptosis
	There can be focal superficial erosions of the surface mucosa
Severe ACR—Grade 3	A marked degree of crypt damage and destruction with crypt loss, there is diffuse mucosal erosion and/or ulceration with marked diffuse inflammatory infiltrate
	If extended severe rejection exists, there is complete loss or the morphology of the bowel with granulation tissue and even fibropurulent exudate, with mucosal sloughing
	The latter changes would be endoscopically defined as "exfoliative" rejection (ER) [37]
	ER has high risk for graft loss and increased mortality in children

down-regulated during ITx rejection and were selected for and achieved technical quantitative reverse transcription polymerase chain reaction replication. Down-regulation of the immunoglobulin (Ig)A+ plasma cell-specific CCR10 gene correlated with decreased mature mucosal CD138+ plasma cell numbers in corresponding biopsy specimens ($r = 0.761$, $p = 0.006$) and inversely correlated with enhanced allo-reactivity of CD154+ T-cytotoxic memory cells ($r = -0.56$, $p = 0.031$), that predict acute cellular rejection with high sensitivity, concluding that protracted depletion of the mucosal CD138+ plasma cell barrier and early mucosal infiltration with memory IgG+ cells characterize the rejection-prone intestine allograft and that mucosal IgA+ plasma cell barrier reconstitution may augment resolution of ITx rejection [36].

To screen for ACR, patients are left with an ileostomy to have access to frequent intestinal biopsy samples. The most commonly used protocol is to take ileal biopsies twice weekly for the first month, then once a month or when symptoms of rejection develop for 3–6 months until stoma closure. There are instances when symptoms are compatible with rejection, but ileal biopsies show no evidence of rejection. If the clinical suspicion is high, the patient should undergo upper endoscopy with proximal small bowel biopsies. The pathologic criteria of ACR were formulated by consensus at the 8th International Small Bowel Transplantation Symposium in 2003 [37] (Table 3).

Currently, there is no reliable biomarker to identify ACR in a non-invasive way. Plasma citrulline (amino acid primarily produced by the enterocyte) and fecal calprotectin (cytosolic protein from the s100 family of proteins) have been studied widely as markers of ACR. Low level of plasma citrulline, is a sign of cell damage, but does not differentiate between ACR, infection, GVHD or PTLD [38]. Levels of less than 20 mmol/L are well correlated with the presence of ACR and levels <10 mmol/L might indicate moderate to severe rejection [39]. Calprotectin is found in neutrophil cytoplasm and can be detected in stools in the setting of active inflammation; however, in the setting of intestinal transplant it has significant inter-patient variability which makes it difficult to define a suitable "cut-off" value. Patients experiencing ACR have greater fluctuations in calprotectin levels than those without; however, routine stool calprotectin monitoring is not strongly supported [40].

When ACR is diagnosed, immediate treatment should be initiated. In general, mild to moderate ACR can be controlled with pulse steroids and increased targets of tacrolimus, whereas patients with moderate to severe rejection should receive pulse steroids and anti-thymocyte globulin. Anti-Tumor necrosis factor-α antagonist, has been used as salvage therapy in refractory ACR [41].

As most of the patients who receive IT have previously had multiple blood transfusions, they are sensitized and at risk of developing donor specific antibodies (DSA) causing antibody mediated rejection (AMR) responsible for refractory ACR, graft loss and chronic rejection. Patients who are sensitized with DSA, have >20 % panel reactive antibodies (PRA) and a positive cross-match have a very poor outcome [42]. Some centers are performing virtual cross-match with the attempt to minimize AMR and improve graft outcome [43]. The goal of the treatment for AMR is to eliminate and inhibit circulating antibodies. Monoclonal antibody against B- lymphocyte CD20 receptor (Rituximab) and plasmapheresis with immunoglobulin (IVIG) have been used with success [42]. Recently Fan et al. reported a case of an adult successfully treated for AMR with Eculizumab (humanized monoclonal antibody
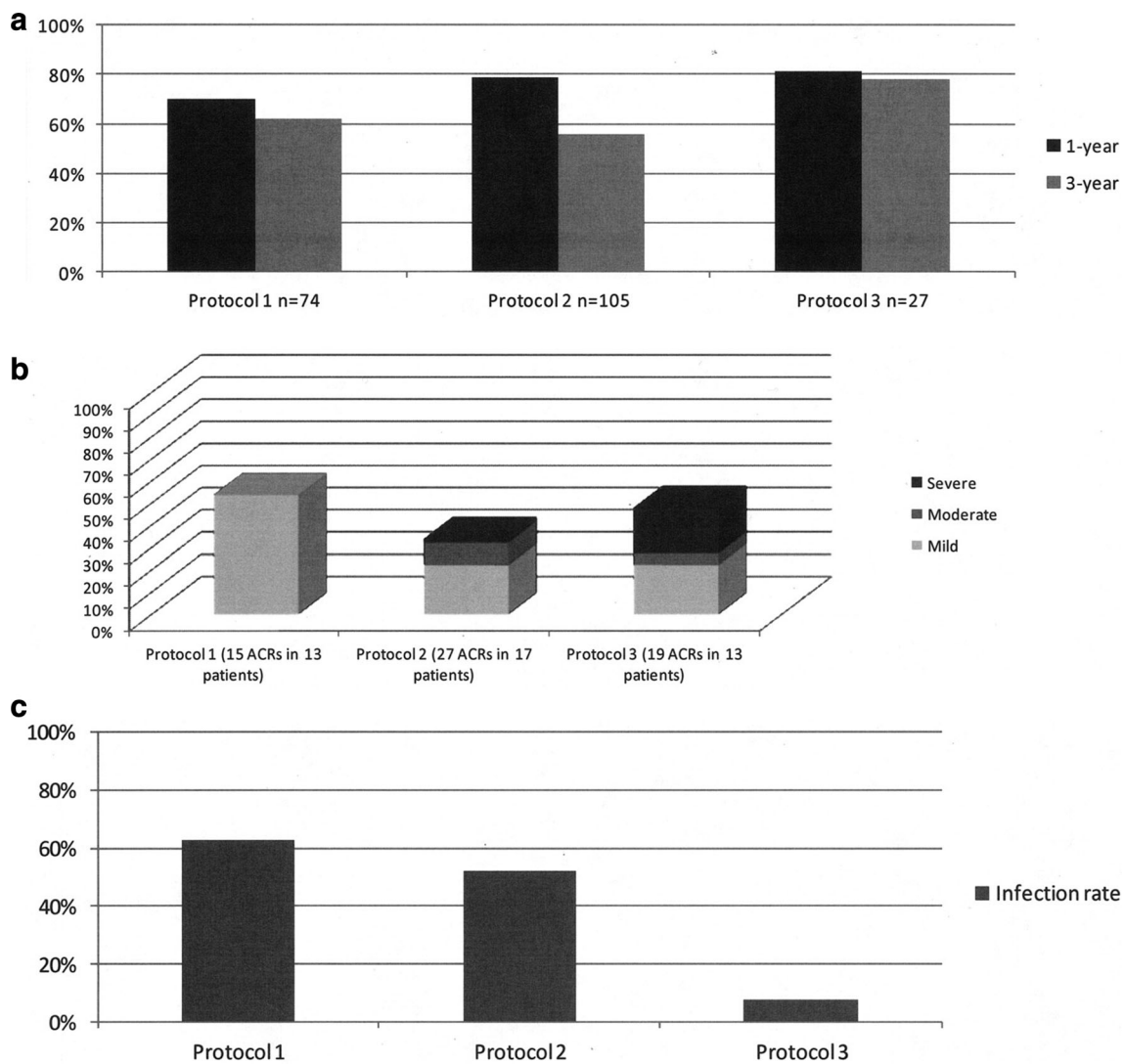
Fig. 5 Immunosuppression protocols. a Patient survival rate, b ACR rate, and c infection rate by immunosuppression protocol

against complement (C5) that has been used in AMR in kidney transplantation [44].

Immunosuppression

Immunosuppression therapy is divided into an induction phase and maintenance phase. It has evolved greatly over the last 20 years. The first immunosuppressive agent used was cyclosporine which was associated with high rejection rates and fatal infectious complications. Outcomes changed greatly after the introduction of tacrolimus in 1990 [45]. Protocols vary amongst transplant centers, but since 2009 when electronic intestinal transplant registry data entry began, most patients (72 %) were induced with either an IL-2 blocker, an anti-lymphocyte product or monoclonal anti-CD52 antibody. The majority of current survivors (92 %) are taking tacrolimus as maintenance immunosuppression. Fifteen percent of the

current survivors are also taking an mTOR inhibitor [1]. A literature review by Trevizol et al., showed 3 main protocols were used in major intestinal transplant centers between 2006 and 2010: Protocol 1—daclizumab induction with tacrolimus and steroid for maintenance; Protocol 2—alemtuzumab for induction and tacrolimus for maintenance treatment; and Protocol 3—thymoglobulin and rituximab for induction and tacrolimus for maintenance. Protocol 2 showed the lowest rate of ACR of 34 % compared to 54 and 48 % for protocols 1 and 3, respectively. Protocols 1 and 2 showed infection rates of 62.5 and 52 %, respectively. One-year patient survival rates were 70, 79 and 81 %, respectively. Three-year patient survival rates were 62, 56, and 78 % for protocols 1, 2 and 3, respectively. Concluding that Protocol 3 (thymoglobulin and rituximab and tacrolimus) seems to be the best available one balancing ACR and infection rates (Fig. 5) [46]. Alemtuzumab has been associated with respiratory life threatening

respiratory complications like ARDS in younger children, therefore should be used with caution in patients less than 4 years [47].

Chronic rejection

Graft and patient survival rates have improved significantly over time (Fig. 6; $p < 0.001$); however, 1-year conditional survival has not improved (Fig. 7; $p = 0.094$). The 5-year survival was approximately 20 % before 1990, and it thereafter increased to over 40 % in the early 2000s and continues to plateau around 50–60 % (Fig. 8). Individual high volume transplant centres may present higher survival rates. For patients transplanted since 2000, actuarial patient survival was 77 % at 1 year, 58 % at 5 years, 47 % at 10 years, while graft survival was 71, 50 and 41 %, respectively. An 8 % re-transplantation rate was observed, second/third graft survival was 56 % at 1 year and 35 % at 5 years. The etiology for graft loss and patient death have not changed over time. Sepsis remains the leading cause of graft loss accounting for over 50 % of cases, followed by
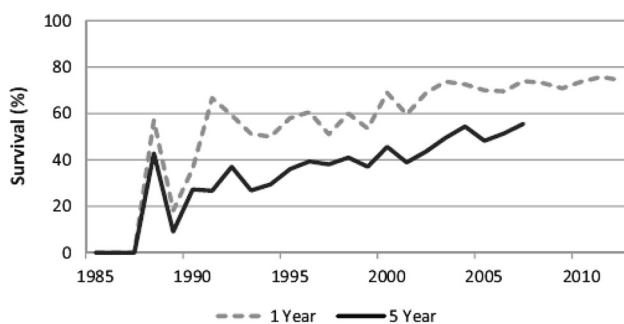

Fig. 6 A times series analysis of the 1- and 5-year actuarial graft survival shows significant improvement over time ($p < 0.001$)
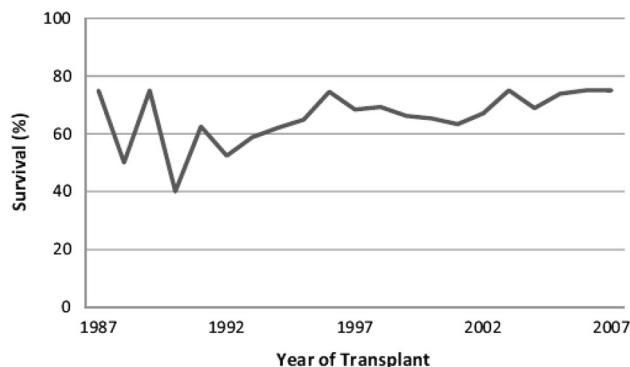

Fig. 7 A time series analysis of overall conditional 5-year actuarial graft survival (defined as graft survival after 1-year) shows little change over time

graft-related causes including rejection (13 %) and cardiovascular events (8 %) [1].

Chronic rejection (CR) is the most common cause of late onset graft dysfunction, and is manifested by increased stoma output or diarrhea despite maximal medical therapy. The cause of CR is multifactorial, but patients with recurrent or severe AR, or recipients of isolated IT are at higher risk for CR [48]. Typical endoscopic and radiographic features of chronic rejection include loss of mucosal folds, focal ulcers and mural thickening, and pruning of the mesenteric arterial tree, respectively [49]. The diagnosis of chronic rejection is confirmed histopathologically by recognizing the obliterative arteriopathy changes in the submucosa, subserosa, and in the mesentery immediately adjacent to the bowel wall [48].

Infections

Sepsis is the most frequent cause of death after intestinal transplantation. Patients are susceptible to viral, bacterial and fungal infections. Bacterial bloodstream infections occur in more than two-thirds of intestinal transplant recipients and are associated with a 15 % lower patient survival at 1 year than intestine recipients without bacterial infections. The source of infection is the central venous catheter in 50 % and intra-abdominal sources in 33 %. *Enterococcus* spp are the most frequently isolated organisms.

Viral infections include cytomegalovirus (CMV), Epstein Barr virus (EBV), adenovirus and calcivirus. CMV viremia has been reported in 11 % and CMV disease in 7 % of pediatric intestinal transplant recipients. For patients who develop CMV disease, there is a high rate of relapse and an 11-fold increased risk of post transplant death [50]. As symptoms of viral enteritis are difficult to differentiate from acute rejection, biopsy evaluation is warranted to conduct PCR on the tissue and histological evaluation that may show mononuclear infiltrate adjacent to the bowel lumen and superficial apoptosis. These changes are detected in the native bowel as well [51]. The highest risk for acquiring CMV infection is to transplant a CMV positive allograft into a CMV-naïve recipient. The mainstay for prophylaxis is to receive intravenous ganciclovir and CMV immune globulin for 3–12 months post IT with routine screening of serum CMV PCR.

Post transplant lympho-proliferative disorder (PTLD)

PTLD is a proliferative disorder of B-lymphocytes driven by EBV. This is the most common malignancy after intestinal transplantation, occurring in 13 % of recipients [52], and, hence the reason why EBV surveillance through
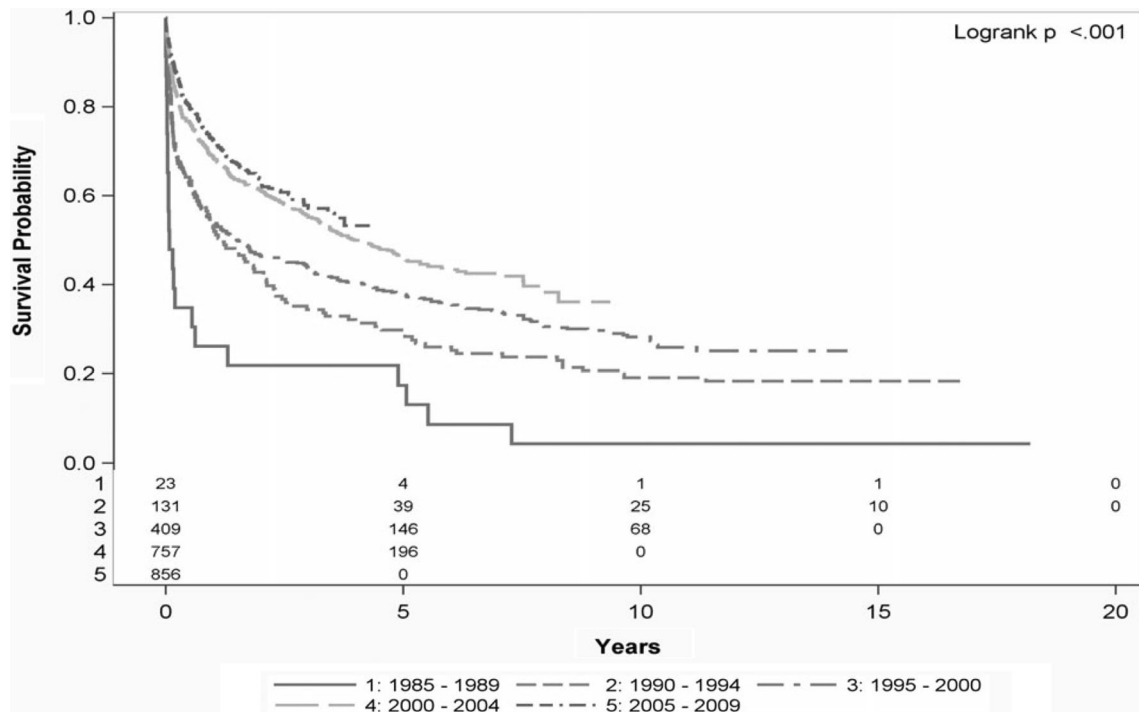
Fig. 8 Survival by era

EBV PCR serum samples is important post transplant. PTLD can manifest with diarrhea, weight loss, enlarged lymphoid mass (adenoids, tonsils, lymphatic nodes, lungs, gut and mesentery). Early detection and treatment with reduction of immunosuppression or combination of the latter and Ganciclovir in cases of high EBV viral load, has decreased the incidence of PTLD to 5–10 % [35].

Quality of life

Survival after IT has improved over the last decades due to advances in surgical technique and management of immunosuppression; however, due to the high incidence of rejection, it is thought that quality of life (QOL) after IT is poor. Few studies have addressed QOL after IT. Peroni et al. in 2012 published data from a preliminary cross sectional study assessing QOL on home parenteral nutrition and after intestinal transplantation using comparable questionnaires. The treatment-specific quality of life questionnaire for adult patients on home parenteral nutrition was adapted for intestinal transplant recipients. Both instruments were composed of 8 functional scales, 9 symptom scales, 3 global health status/quality of life scales and 2 single items. Intestinal transplant recipients showed a better score in following scales: ability to holiday/travel ($p < 0.001$), fatigue ($p = 0.022$), gastrointestinal symptoms ($p < 0.001$), stoma management/bowel movements ($p = 0.001$) and global health status/quality of life

($p = 0.012$). A better score for ability to eat/drink ($p = 0.070$) and a worse score for sleep pattern ($p = 0.100$) after intestinal transplantation were also observed [53]. A recent study published by Andres et al. in 2014 aimed to determine Health related quality of life (HRQOL) after pediatric intestinal transplantation. Thirty-one IT survivors from 1999 to 2012 were asked to complete age-specific HRQOL non-disease-specific questionnaires: TAPQOL (0–4 year), Revidierter Kinder Lebensqualitatsfragebogen (KINDL-R) (5–7; 8–12; 13–17 year), and SF-36v2 (>18 year). The primary caregivers completed a SF-36 questionnaire and Caregiver Burden Interview (CBI). Highest scores were obtained for vitality (group I), self-esteem (group IV), and physical and social functioning and emotions (group V). Lowest scores were obtained in appetite and behavior (I), family and school (III), and chronic disease perception (III, IV). No significant differences were found between caregivers and their children. CBI showed stress in 52 %. SF-36 for caregivers was lower than the general population. No significant differences were found depending on relevant clinical and socio-demographic data. HRQOL was acceptable and improved with age and time since transplantation. It seems that parents have a slightly worse perception of their childs health and also worse perception or their own QOL compared to the general population, and attention should also be paid to them. These results support the idea that when successful, intestinal transplantation

allows a more normal life in most patients and can be offered as an attractive option, as patients are able to join society and perform age-appropriate activities and occupation [54].

The cost of home total parenteral nutrition versus intestinal transplantation is similar during the first year after intestinal transplantation. The incidence of re-hospitalization appears two to threefold more common after transplantation than for patients on PN; however, beyond the first year, the yearly cost of hospitalization and immunosuppressive medication is less after transplantation than the cost of continued PN. This suggests that, if a patient maintains a functional graft, intestinal transplantation becomes cost effective within 1–3 years after the procedure [55].

Summary

Intestinal transplantation (IT) is the least common form of organ transplantation, however, there has been progress in patient and graft survival rates over the past decade. It remains on the continuum of care for pediatric patients with intestinal failure, but bowel transplant rates have declined worldwide over the last 6 years, in large part due to the development of multidisciplinary intestinal rehabilitation programs and the control of progressive cholestatic liver disease with novel lipid-based management strategies. With improved clinical outcomes of pediatric patients with intestinal failure, there is increasing evidence that the current indications for bowel transplantation no longer apply and need revision. The role of bowel transplantation may be changing in pediatric intestinal failure, but it remains an important option. All intestinal rehabilitation programs should have a close and fluid relationship with an intestinal transplant program to ensure early referral and assessment as necessary. The ultimate goal of management of patients with IF is to achieve enteral autonomy and wean PN, reduce mortality, minimize co-morbidity and optimize quality of life. Fortunately, most pediatric patients with IF will eventually become enterally autonomous due to inherent gut growth potential, but some may not, or may develop progressive complications and transplantation is most appropriate [56]. Unfortunately, there has been little advance in long-term survival related to chronic rejection, infection and PTLD. It is this obstacle where further research needs to focus.

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