



REVIEW

Current status of intestinal and multivisceral transplantation

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Abstract

Clinical-nutritional autonomy is the ultimate goal of patients with intestinal failure (IF). Traditionally, patients with IF have been relegated to lifelong parenteral nutrition (PN) once surgical and medical rehabilitation attempts at intestinal adaptation have failed. Over the past two decades, however, outcome improvements in intestinal transplantation have added another dimension to the therapeutic armamentarium in the field of gut rehabilitation. This has become possible through relentless efforts in the standardization of surgical techniques, advancements in immunosuppressive therapies and induction protocols and improvement in postoperative patient care. Four types of intestinal transplants include isolated small bowel transplant, liver-small bowel transplant, multivisceral transplant and modified multivisceral transplant. Current guidelines restrict intestinal transplantation to patients who have had significant complications from PN including liver failure and repeated infections. From an experimental stage to the currently established therapeutic modality for patients with advanced IF, outcome improvements have also been possible due to the introduction of tacrolimus in the early 1990s. Studies have shown that intestinal transplant is cost-effective within 1–3 years of graft survival compared with PN. Improved survival and quality of life as well as resumption of an oral diet should enable intestinal transplantation to be an important option for patients with IF in addition to continued rehabilitation. Future research should focus on detecting biomarkers of early rejection, enhanced immunosuppression protocols, improved postoperative care and early referral to transplant centers.

Key words: intestinal transplant; multivisceral transplant; parenteral nutrition; intestinal failure; gut rehabilitation

Introduction

Intestinal and multivisceral transplantation has evolved from a rare therapeutic modality to a currently life-saving armamentarium for a subset of patients with intestinal failure (IF) [1]. However, as the largest lymphoid organ in the body, the small intestine has posed a significant challenge for transplant survival due to allograft rejection. Meanwhile, with the introduction of tacrolimus in 1989, the field has witnessed substantial growth and interest as a rescue therapy for patients with IF

[1,2]. Paralleled by the developments in transplantation and immunosuppression, gut rehabilitation and nutritional autonomy via pharmacologic and surgical methods have also flourished including autologous surgical reconstruction and new enterocyte trophic factors. Concurrently, parenteral nutrition (PN) has become the first-line treatment for patients with IF and a bridge for patients awaiting transplantation [3].

Despite complexities in gut transplantation, the 1-year, 5-year and 10-year graft survivals were 74%, 42% and 26%,

respectively (for intestine); 70%, 50% and 40%, respectively (for simultaneous intestine, liver, and pancreas transplant); and 61%, 46% and 40%, respectively (for combined intestine and liver) [4–7]. This is due to continued innovations in surgical techniques, postoperative management and immunosuppressive strategies. Furthermore, the organ procurement and transplantation network reported that between 1990 and 2013, a total of 2379 intestinal transplants were performed, with >500 transplants at a single center: the University of Pittsburgh [4–6]. Additionally, visceral transplant activities have increased simultaneously in all continents except Africa, the reason for which is unclear [6].

In this review, we discuss the various complexities of intestinal and multivisceral transplantation with an in-depth view of the historical challenges, current trends and controversies as well as future prospects of intestinal and multivisceral transplantation. We also provide an overview of intestinal failure, gut rehabilitation, indications for transplant and postoperative care of transplant patients.

Intestinal failure

IF—or loss of nutritional autonomy—is defined as the inability of enterocytes to absorb essential nutrients, water, electrolytes, vitamins and minerals and is commonly caused by malabsorption, obstruction or motility disorders [8]. As fluid, nutrient and electrolyte absorption are directly related to the absorptive length of the small intestine, any reduction in the enterocyte cell mass will result in suboptimal absorption. The most common causes of IF can be categorized into pediatric and adult etiologies. In the pediatric population, congenital disorders such as gastroschisis (with less common causes including necrotizing enterocolitis, volvulus and microvillus inclusion disease) are the leading causes of IF [9]. In the adult population, mesenteric vascular thrombosis and inflammatory bowel disease are the most common causes of IF in addition to radiation enteritis, desmoid tumors and trauma [9]. IF can also result from short bowel syndrome (SBS) defined as < 200 cm of residual small intestine due to multiple resections or single resection of significant bowel length [10]. Despite these diverse etiologies, the majority of patients with decompensated IF are dependent on PN to maintain fluid, electrolyte and nutritional homeostasis [10].

Intestinal adaptation

In response to extensive intestinal resection, there is significant adaptation of the remnant bowel to enhance nutrient absorption [11]. Villus diameter and height increase to enhance the absorptive surface area of the residual small intestine approximately 1–2 years after intestinal resection [12]. However, limited data exist to elucidate the exact underlying mechanism of this adaptation. Intestinal adaptation depends on factors such as health of remaining bowel, residual colonic length, location of resection (duodenum, jejunum or ileum), enteral nutrients and enterotrophic factors [12]. Of these, enteral nutrients are the most important stimuli for the adaptive mechanisms that include increase in epithelial surface area, gastric secretion, gastric emptying and intestinal transit [13]. Additionally, there is increased expression of the peptide transporter Pep T1 in the remaining colon in patients with small bowel syndrome. The need for patients to consume excessive amounts of complex food may be particularly necessary due to the important role of luminal nutrients in the adaptation process, [13]. Furthermore, studies demonstrate that approximately 100 cm

(without colon) or 60 cm (with functional colon) of intestinal tissue are required for PN independence; however, individual and patient-specific factors may also play an important role in the ability of the enterocytes to adapt [14].

Intestinal rehabilitation: behavioral, pharmacological, and surgical innovations

The care of patients with IF is remarkably complex and is dependent upon the efficient involvement of a multidisciplinary team that includes—but is not limited to—a gastroenterologist, surgeon, dietitian, social worker and psychiatrist. Patients often require bowel rehabilitation and/or PN prior to intestinal transplantation depending on residual bowel length, function and nutritional status. Innovative therapeutic modalities (such as dietary modification, enterocyte growth factors and surgical rehabilitation including autologous reconstruction and bowel-lengthening procedures) have been introduced to treat patients with IF. [15–17].

Intestinal rehabilitation is defined as the process of restoring nutritional autonomy in patients with IF to enteral feeding with a goal of weaning PN therapy [18]. Diet modification is the first-line therapy and includes hyperphagia with consumption of small frequent meals consisting of complex carbohydrates and protein with or without fat restrictions (depending on the presence or absence of colon) to deliver the necessary luminal growth factors [17]. Soluble fibers may also be beneficial, both as a source of energy as they are metabolized to short chain fatty acids in the colon and also because they can help increase the viscosity of stomal effluent [19]. Furthermore, patients with SBS may need vitamin and mineral supplements in excess of the dietary references [19].

Pharmacological therapy is used to decrease intestinal transit and improve absorption. Antidiarrheal medications including diphenoxylate-atropine, loperamide, codeine and opium tincture reduce high-output states and may prevent dehydration. Similarly, octreotide may improve secretory diarrhea and histamine-2 receptor antagonists (H₂RAs) or proton pump inhibitors are used to decrease gastric acid hypersecretion [20]. Probiotics and antibiotics can be used to prevent or treat small bowel bacterial overgrowth [21]. Recently, omega-3 lipid formulations have replaced the standard omega-6 lipids across several IF programs worldwide due to their anti-inflammatory properties and to prevent parenteral nutrition-associated liver disease (PNALD), but they have yet to become the standard of practice in the USA [22]. Furthermore, in addition to nutritional support, enterocyte growth factors have recently been introduced to promote the natural process of gut adaptation [23]. Teduglutide or recombinant human glucagon-like peptide-2 (GLP2) was approved in the USA in 2012 (Gattex; NPS Pharma, Bedminster, NJ) as a targeted treatment for IF. Teduglutide was shown to reduce the need for PN requirements in SBS-induced IF patients [24]; it also inhibits gastric emptying and increases intestinal transit time, thereby increasing the exposure of luminal growth factors to enterocyte cells [25]. Lastly, surgical gut rehabilitation including autologous surgical reconstruction (foregut reconstruction, auto-transplantation) and bowel lengthening techniques (Bianchi's procedure, serial transverse enteroplasty [STEP procedure]) are significant advances in the surgical management of gut failure [26–28].

Parenteral nutrition: indications and complications

PN, which was first available in 1968, has traditionally been used for patients with malnutrition secondary to IF in settings

such as intensive care units, nursing homes, hospital wards and patients' homes [29]. It is often a life-saving measure after enteral feeding has failed to provide essential nutrients for these patients. In fact, the purpose of PN in IF patients has been to improve nutritional status and reduce the rate of nutrient-related hospitalizations such as dehydration and electrolyte disturbances [29]. Approximately 50–75% of these patients with IF are eventually weaned from PN within 2 years of onset due to the natural adaptation process of the remaining intestine [30]. However, depending upon the adaptation process, some of these patients may require PN or, in some cases, specialized intravenous fluids for life [30].

PN therapy is associated with short-term and long-term complications that may limit their prolonged use in many patients with IF [31]. Short-term complications are catheter-related blood stream infections (CRBSI) and catheter-related mechanical complications. Long-term complications include liver failure and metabolic bone disease. Approximately, 5% of all deaths in patients requiring PN are attributed to CRBSI [31]. Coagulase-negative staphylococci and streptococci are the predominant organisms causing CRBSI [31]. The most common complication of long-term PN therapy is PNALD, which is more common in pediatric patients with IF and has a mortality rate of up to 15% [32]. It is estimated that approximately 55% of patients who received PN for more than 2 years developed chronic cholestasis [32]. Histological features of PNALD include steatosis, fibrosis, cholestasis or cirrhosis [33]. Lipid emulsions likely play an important role in the etiopathogenesis of PNALD, and their use should be minimized [34]. Further, cyclical infusions of PN may help reduce the risk of PNALD by limiting constant exposure of PN metabolites to the liver [34].

Other complications of PN include central venous access thrombosis, metabolic bone disease, fluid overload and electrolyte imbalances [10]. One study of 124 adult SBS patients reported survival and PN-dependence probabilities of 86% and 49% and 75% and 45% at 2 and 5 years, respectively [35].

Therefore, regular monitoring for these complications is critical for patients on long-term PN.

Despite the novel therapeutic modalities available for patients with IF including PN, the choice of therapy for patients with IF is highly individualized, and factors such as patient age, function of residual intestine, patency of splanchnic vasculature, restoration of gastrointestinal continuity and preservation of ileocecal valve play a pivotal role in successful rehabilitation [8]. Failure of the modalities discussed herein to maintain nutritional status should prompt consideration for visceral transplantation. One study of 59 patients with IF reported that those with indications who underwent early transplant had higher survival rates than those patients who did not receive a transplant [17]. Moreover, long-term PN therapy resulted in increased mortality in patients awaiting transplant. We believe that these results stress the importance of individualized care for patients with IF and timely referral for visceral transplantation to achieve better long-term survival and quality of life outcomes.

Historical trends of intestinal and multivisceral transplantation

The development of intestinal and multivisceral transplantation is a significant milestone and has revolutionized the field of gut rehabilitation (Figure 1). For decades, abdominal visceral transplantation was a significant clinical challenge because of immunologic, anatomic and functional complexity; the challenges also included the massive lymphoid load and bacterial colonization of the gut [36]. However, with the landmark investigations of Dr. Starzl and Dr. Lillehei in the 1960s, it was evident that the greatest obstacle in intestinal and multivisceral transplantation would be graft rejection and infectious complications [37,38]. With the discovery of cyclosporine and then FK506 (Prograf, tacrolimus) in 1989, transplantation became an important option for IF patients. Compared with cyclosporine, tacrolimus gave physicians better ability to help prevent rejection and adjust doses in a timely fashion [39].

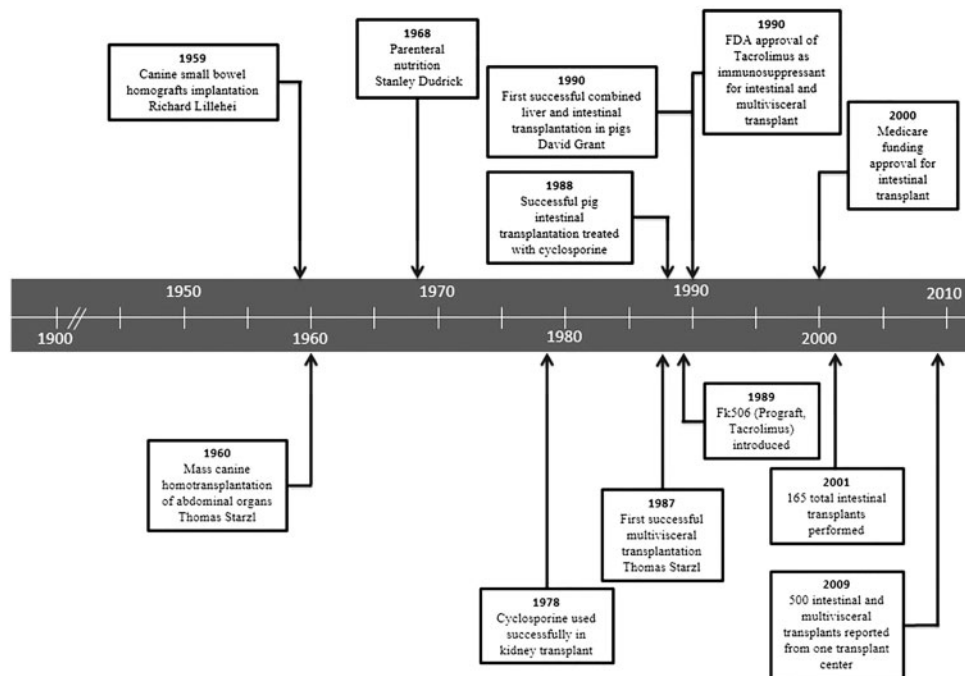


Figure 1. Historical timeline of the development of intestinal and multivisceral transplant

Table 1. Centers for Medicare and Medicaid approved indications for intestinal transplantation [42]**Failure of parenteral nutrition**

- Impending (total bilirubin 3–6 mg/dL, progressive thrombocytopenia and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis or cirrhosis) because of parenteral nutrition-liver injury.
- Central venous catheter-related thrombosis of 2 central veins.
- Frequent central line sepsis: 2 episodes/year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungemia; septic shock or acute respiratory distress syndrome.
- Frequent episodes of severe dehydration despite intravenous fluid in addition to parenteral nutrition.

High risk of death attributable to the underlying disease

- Desmoid tumors associated with familial adenomatous polyposis.
- Congenital mucosal disorders (e.g. microvillus atrophy and intestinal epithelial dysplasia).
- Ultra-short bowel syndrome (gastrostomy, duodenostomy, residual small bowel 10 cm in infants and 20 cm in adults).

Intestinal failure with high morbidity or low acceptance of parenteral nutrition

- Intestinal failure with high morbidity (frequent hospitalization, narcotic dependency) or inability to function (e.g. pseudo-obstruction, high output stoma).
- Patient's unwillingness to accept long-term parenteral nutrition (e.g. young patients).

Interestingly, there has been a steady decline of transplant activity in the USA (SRTR data) with a peak in 2007 [40]. Perhaps this is due to recent growing interest in non-transplant gut rehabilitation, regulatory measures, economic status and reduction in incidence of nutritional failure secondary to PN. However, with the recently reported increased mortality rates of waiting liver-intestine recipient candidates compared with liver-only recipients, the United Network for Organ Sharing (UNOS) allocation policy recently allowed more widespread access to the national pool for adult liver-intestinal candidates.

Indications for intestinal and multivisceral transplantation

The most common reason for intestinal and multivisceral transplantation is SBS. Despite the significant improvement in patient survival, the procedure is still limited to patients who have experienced significant complications of PN and/or repeated nutritional failure with dehydration or electrolyte imbalance. Most physicians also require failed attempts at gut rehabilitation prior to referring patients to transplant centers [41]. The indications for intestinal transplantation approved by the Centers for Medicare and Medicaid services for reimbursement are listed in Table 1 [42]. A 3-year prospective study that evaluated these approved indications concluded that intestinal transplantation is an appropriate life-saving measure for IF patients after failure of PN therapy [43]. Of note, European prospective data further suggested that recurrent infection may not be associated with definitive PN failure and may not warrant transplantation [44]. In addition, because of the current lack of effective rehabilitative surgery for disorders such as certain enterocyte dysfunction, gut dysmotility and Gardner syndrome, early transplantation may be necessary. Regardless of the indications for transplant, recently published data have stressed the importance of early transplantation, perhaps prior to overt PN-induced liver disease and possibly within 1 year of use of pre-transplant PN for better survival [45].

Types of gut transplantation

The type of transplantation depends on the underlying etiology of IF, quality of native organs, presence/severity of liver disease and history of prior abdominal surgeries. Despite the variety of nomenclature in literature, fundamentally there are 4 types of

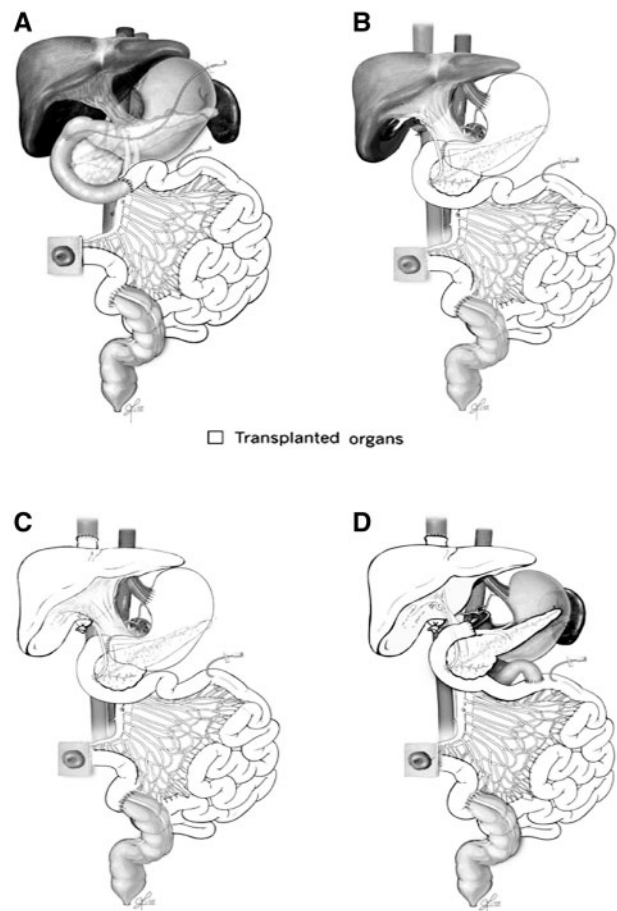


Figure 2. Main types of visceral transplantation. A) Intestine alone. B) Modified multivisceral transplant with exclusion of the liver. C) Full multivisceral transplant that includes stomach, duodenum, pancreas, intestine and liver. D) Combined liver and intestine with pancreas.

gut transplantation: isolated small bowel transplant, liver-small bowel transplant, multivisceral transplant and modified multivisceral transplant (Figure 2). Post-transplant survival rates may be higher for combined liver/intestine recipients compared with isolated intestine recipients due to proven immunologic benefits of the liver [4,46,47]. However, most patients with SBS,

pseudo-obstruction and Gardner syndrome receive isolated intestinal or modified multivisceral transplantation [48]. Additionally, recent data have suggested that hepatic fibrosis may not be an absolute contraindication for isolated intestinal transplant as 4 patients with significant portal and centrilobular fibrosis had regression of their liver disease after intestine-only transplant [49].

Surgical innovations

Recent innovations in both donor and recipient operations have allowed intestinal and multivisceral transplantation to become one of the life-saving treatment modalities for patients with IF and nutritional failure. In the donor operation, the simultaneous retrieval of both the intestine and pancreas to benefit two different recipients has been a significant advance [50]. Additionally, to reduce biliary surgical complications, *en bloc* preservation of the donor pancreaticoduodenal complex with combined liver-intestine was successfully introduced in 2011 for patients with Gardner syndrome [51]. Furthermore, to reduce infections, inclusion of the donor spleen was employed in 1 study that compared primary multivisceral recipients who received a donor spleen (N = 60) to those who did not receive a spleen (N = 81); no significant differences in infectious complications between the spleen and control groups were reported. Furthermore, platelet and leukocyte counts became normal in splenic patients, whereas these counts were significantly increased in nonsplenic recipients [52]. Colonic retrieval *en bloc* and distal esophagus retrieval *en bloc* were also initiated to reduce rates of complications from existing multivisceral transplantation [53,54].

In recipient operations, major surgical innovations such as preserving native pancreas and portosplenic circulation have decreased the need for biliary reconstruction and augmentation of islet cell mass. Another major technique that was introduced in patients with preserved liver functions, especially those with Gardner and pseudo-obstruction syndromes, is preservation of the native liver, spleen and pancreaticoduodenal complex to theoretically reduce the rate of post-transplant lymphoproliferative disorder (PTLD) [55].

Suboptimal closure of the abdominal wall post transplant has been a major concern for surgeons. Due to multiple surgeries, scar formation, infectious complications and visceral allograft tissue edema, loss of the abdominal domain has become a surgical challenge in transplant patients [56]. Recent innovations such as implantation of tissue expanders prior to transplant, acellular dermal allograft, simultaneous vascularized abdominal wall and non-vascularized rectus fascia transplant have reduced complications associated with an open abdomen [57]. *In situ* pre-placement of free vascular grafts, duct-duct biliary reconstruction and piggyback duodeno-duodenal anastomosis in patients with preserved native duodenum are other novel implantation techniques that have been introduced [58].

Postoperative care

Despite the varying postoperative protocols followed between centers, effective postoperative management is critical for transitioning transplant patients to attain clinical nutritional autonomy (CNA) [59]. Early CNA has been shown to improve enterocyte recovery and prevent gut barrier dysfunction. With the discovery of molecular diagnostic techniques and newer antimicrobial agents, improved postoperative care has reduced rates of rejection, infection and mortality. Reduction in the requirement of maintenance immunosuppression, availability of

the polymerase chain reaction for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) monitoring have all reduced the risks of PTLD, CMV and fungal infections in patients with visceral transplantation [60]. Furthermore, the transition from transplantation to CNA has proven to be very complex and has required a stepwise weaning protocol from PN to CNA averaging about 57 days. Enteral feeding is often initiated when allograft motility and function have been established. The D-xylose absorption tests as well as clinical, radiological and histopathological analyses have been utilized to assess CAN [61]. Also, data from the 2003 report of the intestine transplant registry, which included 61 programs with 989 grafts in 923 patients, reported that > 80% of all current survivors had stopped PN and resumed normal daily activities [62].

Immunosuppression

The field of intestinal and multivisceral transplantation has experienced significant obstacles due to the risk of destructive alloimmunity [63]. Global efforts are being established, with unique immunosuppressive strategies to overcome such challenges. Despite implementing a tacrolimus-steroid immunosuppression strategy, high rates of acute and chronic rejection were observed, resulting in high mortality rates until 1994. However, newer immunomodulatory strategies have emerged in 1995 such as bone marrow cell infusion and low-dose allograft irradiation as well as the regular use of induction therapy (cyclophosphamide, daclizumab) [64] (although the long-term benefit of such strategies was limited due to the continuing requirement for long-term immunosuppression therapies). In 2001, it was thought that conventional immunosuppressive therapies could potentially mask the seminal mechanisms of long-term alloengraftment [65]. The concept of recipient preconditioning with partial lymphoid depletion to decrease the initial alloimmune response was introduced as the Pittsburgh Protocol.

The Pittsburgh Protocol consisted of pretreating patients with 1–2 grams of steroid bolus in addition to single infusion dose of rabbit antithymocyte globulin (rATG, 5 mg/kg body weight) or alemtuzumab (campath-1H, 30 mg; Genzyme Corporation); the patients also received tacrolimus monotherapy post transplant (trough level: 10–15 ng/mL) [65]. Additional, maintenance steroids were only prescribed for a specific subset of patients. Early attempts at reducing maintenance immunosuppression have demonstrated that approximately 57% of patients could be successfully weaned from tacrolimus monotherapy if pretreated with lymphocyte-depleting agents. Data also suggested that overall survival was higher in campath-1H treated patients compared with patients who received rATG [65]. The immune cell function assay (immuKnow) has emerged as a potential objective analysis for determining which patients are candidates for tapering post-transplant tacrolimus immunosuppression. Subsequently, mTOR inhibitors such as rapamycin have emerged as possible adjunct maintenance immunosuppressive agents [66]. Other adjunct maintenance therapies attempted include azathioprine and mycophenolate mofetil [67]. We strongly believe that induction of partial tolerance with adoptive regulatory T cells as well as new discoveries of reliable immune tolerance assays will improve drug-free allograft acceptance with minimal maintenance immunosuppression [68].

Transplant complications and outcomes

The most substantial hurdle in the field of intestinal and multivisceral transplantation has been the high rates of acute

visceral allograft rejection [69]. With novel immunosuppression strategies, the risk of allograft rejection has decreased, although it is still significant. Implicating factors include inferior tolerogenicity of the gut-associated immunocytes, dynamic interaction between adaptive and innate immunity and development of harmful alloantibodies. Interestingly, combined liver-intestinal transplants and multivisceral transplants have offered immunologic advantages and decreased graft rejection rates compared with intestinal transplantation alone. Possible explanations include formation of donor-specific antibodies (DSA) early in the post-transplant period. In 79 patients undergoing intestinal/multivisceral transplantation, 28% of patients developed post-transplant DSA. These patients had increased risk of chronic rejection (14% vs 5%) and graft-loss (18% vs 7%), although these results were not statistically significant [70]. The diagnosis of acute cellular rejection is a combination of clinical, endoscopic and histological parameters, with histology being considered the current gold standard. Studies on visual surveillance of intestinal allografts via endoscopic evaluation have concluded that biopsy is mandatory for detecting early, treatable rejection even though visual inspection of grafts is able to detect severe rejection [71]. Serum citrulline and fecal calprotectin have recently emerged as potential reliable noninvasive indicators of acute rejection [72,73]. Furthermore, gut microbiota, proteomics and metabolomics such as pro-inflammatory mediator leukotriene E₄, vitamins B₂, B₅, B₆ and taurocholate may be able to identify bioprofiles associated with intestinal rejection [74,75]. Finally, serial DSA measurement in the post-transplant period may be beneficial in screening for acute rejection [70].

The leading cause of death in transplant patients is infection, with studies indicating that up to 94% of recipients develop a bacterial infection post transplant [76]. Furthermore, factors such as re-transplantation and post-transplant renal replacement therapy were associated with increased risk of infection with opportunistic organisms [76]. In terms of immunosuppressive agents, the use of mycophenolate mofetil has resulted in higher infectious complications compared with other agents [77]. EBV and CMV infections are very common and can result in acute or chronic visceral allograft rejection as well as PTLD. Viral infections such as rotavirus, norovirus and adenovirus have been observed in up to 40% of transplant-rejection patients. However, early detection and prophylaxis of these infections is a substantial achievement in the field of transplantation and has resulted in improved survival and quality of life [77].

There have been significant fears of graft vs host disease (GVHD) in intestinal transplants due to large lymphoid burden. The overall incidence of this complication is 5–7% with a mortality rate as high as 70% [78]. Risk factors for GVHD include younger age, transplantation of multivisceral organs, immune deficiency disorders and history of splenectomy [79]. Additionally, laboratory studies that detect circulating or tissue-invasive donor leukocytes are required for diagnosis of GVHD. These include polymerase chain reaction, *in situ* hybridization, immunohistologic staining of donor-specific human leukocyte antigen and short tandem repeat techniques. Treatment often involves a combination of tacrolimus, steroids and stem cell therapy [79].

PTLD is thought to occur in approximately 20% of all intestinal transplant patients and is associated with EBV infection [80]. Patients without PTLT have significantly higher survival rates with induction therapy and recipient pretreatment. Also, a decrease in PTLT has been observed with early detection and eradication of EBV infections [81].

In certain visceral allograft recipients at long-term follow-up, *de novo* malignancies have been observed. Possible explanations for this observation include prolonged exposure to oncogenes and impaired immune surveillance state [60]. We believe that regular follow-ups with tumor surveillance are effective in the early diagnosis and management of such complex patients.

Other complications that have emerged due to a combination of transplantation and immunosuppressive agents include neuropsychiatric disorders such as depression and anxiety, peripheral neuropathy and micronutrient deficiencies including pyridoxal -5-phosphate, zinc, vitamin E and folate [82].

Patient and graft survival

A large series of 500 intestinal transplants demonstrated a direct, significant correlation between advancements in immunosuppression techniques and graft survival [4]. In particular, reduction in graft rejection, infection and renal failure have been credited for the decrease in mortality rates. However, these complications remain prominent and threatening to the long-term survival of graft function. In 1 study, the persistence of preformed and development of *de novo* DSA was credited as the most significant risk factor for graft survival [69]. Other significant predictors of long-term patient and graft outcome include personal social support as well as inclusion of liver for visceral allograft longevity. Recently, documented patient survival rates include 90% at 1 year, 75% at 10 years and 61% at 15 years. Overall graft survival rates were 59% and 50% at 10 and 15 years, respectively [40]. Improvements in body mass index and high rates of CNA reflect the substantial advancements in the field of intestinal and multivisceral transplantation. In patients who fail to achieve full recovery of allograft motility and function, ischemia reperfusion injury is thought to play a major role, although normothermic *ex vivo* perfusion technology may reverse this unwanted effect [83].

Quality of life

Quality of life has become an essential endpoint for intestinal and multivisceral transplantation. Evidence shows that non-functional social support and quality of life correlate directly with suboptimal patient survival [84,85]. Studies that have compared small intestinal transplantation to PN demonstrate that intestinal transplant patients reported significant improvement in quality of life, functional status, decreased anxiety and sleep difficulties compared with patients on PN [86,87]. In pediatric patients, the child health questionnaire study reported that transplant patients had physical and psychosocial functions comparable to their healthy counterparts. However, a recent study reported lower values in school functioning and psychological health using the Pediatric Quality of Life Inventory instrument [87].

In adults, a cross-sectional analysis of 376 patients regarding health-related quality of life reported high mortality rates among foreign national transplant recipients and nonfunctional social supports [40]. According to Lansky and Karnofsky scores, 85% of current transplant survivors had normal functional status. A high education score and ability to create a nuclear family were valid indicators of increased quality of life for transplant patients [40].

A higher incidence of autism, attention-deficit-hyperactivity disorders and hearing loss was observed (particularly in the pediatric population), which was possibly due to gut and nutritional failure during early phases of neuronal development [88].

We believe that early, aggressive attempts at gut rehabilitation may delay or eliminate these detrimental deficits. Furthermore, prospective quality of life analysis on larger sample sizes is required to update previously reported data.

Cost

Few studies have investigated the cost-effectiveness of intestinal transplantation compared with PN [89–91]. The average cost for nutritional bags excluding the costs of home nursing support, equipment and materials was estimated to be from US\$750 000 to US\$150 000 per year. Furthermore, patients on PN require rehospitalization 0.5–1.0 times/year at a cost ranging from US\$0 to US\$140 000 per year. Compared with PN, the cost of isolated intestinal transplant is estimated to be around US\$132 285. Also, the initial hospitalization for transplantation has been estimated to cost approximately US\$100 000–US\$300 000 with additional costs for complications. Hence, intestinal transplantation is reported to be cost-effective within 1–3 years after the procedure if the patient maintains a functional graft [89]. Another study that simulated the disease course of irreversible IF after PN or intestinal transplant reported that transplant slightly improves survival of patients with IF in comparison with HPN at an additional cost of US\$21 237 per life-year gained [90].

Challenges and current insights

The last 2 decades have witnessed substantial advancements in improving both graft and patient survival as well as the quality of life of patients who undergo intestinal and multivisceral transplantation. Despite these advancements, significant obstacles still remain including visceral allograft rejection, immunosuppression and immunological monitoring and long-term survivability. Many aspects of intestinal and multivisceral transplantation remain to be defined including biomarkers for early rejection, novel immunologic strategies and methods to reduce infectious complications.

We believe that long-term survivability of both the grafts and the patients are dependent on the development of a multidisciplinary team including social assistance. These endeavors are particularly important for patients with lower socioeconomic status and for pediatric recipients to reduce life-threatening behaviors including substance abuse and noncompliance. Monitoring of graft function, tumor surveillance and effective medical management of comorbidities are critical for sustaining long-term survivability. Furthermore, with studies indicating increased mortality rates in patients on the national waiting list, efforts to modify the existing UNOS/Organ Procurement and Transplantation Network (OPTN) allocation system and donor availability should be initiated.

CONCLUSIONS

The field of intestinal and multivisceral transplantation has produced tremendous breakthroughs in terms of immunosuppression, graft and patient survival and postoperative management. As we better understand the intricacies of the transplanted and native organs as well as the potential for stem cell tissue-engineered intestine, we anticipate better long-term survival of patient grafts, nutritional autonomy and decreased reliance on long-term artificial nutrition and its associated complications. Recent data stress the importance of early consideration for gut rehabilitation including transplant, and we strongly recommend that all patients with IF be referred to

tertiary care centers for appropriate management to restore CNA. In summary, abdominal visceral transplantation has become an important option in the therapeutic armamentarium for irreversible IF. We sincerely believe that early referral to intestinal and multivisceral transplantation for patients with IF will afford them the best opportunity to regain CNA.

Conflicts of interest statement: none declared.

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