Gut rehabilitation and intestinal transplantation

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The field of short bowel syndrome and gastrointestinal failure has recently evolved, particularly after the clinical introduction of intestinal and multivisceral transplantation. For nearly three decades, the management of short bowel syndrome was limited to the natural adaptation process and lifelong intravenous supplementation. However, recent clinical availability of intestinal transplantation as an alternative to total parenteral nutrition, has fueled the field with relentless efforts to enhance intestinal adaptation and gut rehabilitation with the achievement of full nutritional autonomy. Intestinal and multivisceral transplantation has added new dimensions as a creative therapy to short bowel syndrome patients, as well as those with extensive abdominal pathology that could not be treated with conventional methods. With continuous improvement in the survival outcome, the procedure has become more widely applicable and commonly utilized, with more than 65 intestinal transplant centers worldwide. With the procedure currently showing improvement in therapeutic indices, including cost effectiveness and quality of life, we believe intestinal and multivisceral transplantation should promptly be offered to short bowel syndrome patients who fail conventional rehabilitation as well as those with complex abdominal pathology.

Keywords: intestinal transplantation, short bowel syndrome, total parenteral nutrition

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In late 1960s, intravenous feeding was introduced to rescue patients who lost most of their small bowel, developed short bowel syndrome (SBS) or could no longer maintain their needs through enteral nutrition [1]. Since then and until 1990 when intestinal transplantation became clinically feasible, little attention has been given to the field of SBS and gastrointestinal failure [2,3]. In the 1970s and 1980s, limited success was achieved to enhance intestinal adaptation and restore the gastrointestinal nutritional autonomy [4–8]. Recent improvement in the therapeutic efficacy of intestinal and multivisceral transplantation has fueled the field and triggered further interest in new innovative therapeutic modalities rather than transplantation. In February of 2004, the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) and the American Society for Parenteral and Enteral Nutrition (ASPEN) jointly organized a workshop on intestinal failure with a special focus on current and emerging therapies including intestinal rehabilitation and transplantation. Similar to other complex diseases, a multidisciplinary therapeutic approach is essential for the optimal management of this unique and orphan population.

Gut rehabilitation

Natural adaptation

Shortly after massive surgical resection, the remaining bowel begins to adapt for functional compensation with a duration of approximately 2 years [9,10]. Luminal nutrients from complex foods are the most potent stimuli with responsive changes including an increase in epithelial surface area, protein expression, gastric secretion, gastric emptying and intestinal transit time. Intestinal hypertrophy rather than enterocyte hyperplasia seems to be the central mechanism of natural adaptation with an increase in villous height. In addition, an upregulation of the peptide transporter PepT1 in the remaining colon was observed suggesting an increase in the luminal transport of simple peptides derived from the diet [11]. The dynamics of the adaptation process and the effect of the therapeutic intervention on the different phases have been conceptually depicted by Jeppesen and colleagues (**Figure 1**) [12].

Rehabilitation

Gastrointestinal tract rehabilitation involves restoration of nutritional autonomy with an unrestricted oral diet and elimination of the need for intravenous nutritional support. A successful outcome is largely determined by the status of the remaining bowel and the implemented diet-based protocol. The clinical availability of a potent enterotropic agent will unequivocally evolutionize the field with significant impact on the clinical outcomes [13,14].

Diet

The diet regimen is an essential component of any therapeutic strategy for intestinal rehabilitation. The recipe reflects the surgical anatomy of the residual gastrointestinal tract, with the aim to maximize absorption and reduce output. Consumption of small frequent meals and avoidance of simple sugars, primarily disaccharides, help to decrease the intraluminal hyperosmotic load. With the colon connected to the proximal bowel, diet should contain 60% complex carbohydrate, 20% protein and 20% fat with no fat restriction in the absence of a functioning colon [15].

Fiber

Patients must utilize viscous or soluble fibers from food sources with additional supplements if needed. With a functional colon, undigested fiber and carbohydrate will be metabolized into short-chain fatty acids with a significant increase in the number of calories being absorbed from the colonic mucosa [16]. In addition, soluble fiber supplements increase the viscosity of the ostomy effluent, if present, and prolong transit time.

Oral rehydration

Maintenance of adequate hydration is achievable using oral rehydration solutions that contain 90 mEq Na/l and 20 m of glucose/l [17]. The solution utilizes the active cotransport system of sodium and glucose molecules at the intestinal brush border [18].

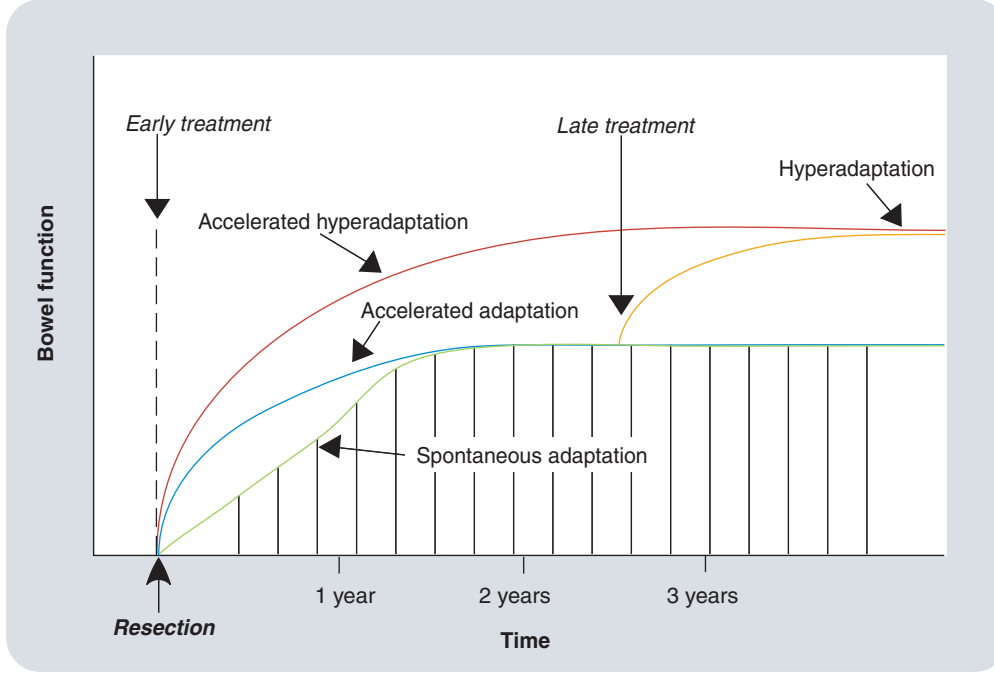
Supplements

Vitamin and mineral deficiencies, particularly vitamin B12, fat-soluble vitamins, calcium, magnesium and zinc, are common in patients with SBS [19]. Often vitamin and mineral supplementation in doses exceeding dietary reference intakes are required to maintain adequate vitamin nutriture.

Pharmacologic therapy

The success of dietary modification can be improved using medications that prolong transit time, reduce secretions and improve absorption. Commonly used antidiarrhea medications include diphenoxylate-atropine, loperamide and tincture of codeine or opium. Octreotide, a somatostatin analog, is used for severe secretory diarrhea, whilst histamine receptor antagonists and proton-pump inhibitors decrease gastric acid secretions and prevent peptic ulceration [20]. Exogenous bile salts are usually added to improve fat and calcium absorption [21]. Gut decontamination and probiotics are often helpful in patients with bacterial overgrowth [22].

Figure 1. Schematic representation of the dynamics and different phases of the intestinal adaptation.



Reprinted with permission from [12].

Tropic factors such as growth hormone and glucagon-like peptide-2 (GLP-2), have been used either alone or in combination with a modified diet, to improve absorption and reduce dependency on parenteral nutrition [13,14]. In December 2003, the US Food and Drug Administration (FDA) approved the use of growth hormone for the treatment of SBS based on the completion of a Phase III randomized, controlled clinical trial [14]. GLP-2 is currently under evaluation in an international, multicenter, controlled study including the author's institution.

Reconstructive surgery

Prompt operative intervention, when indicated, plays a major role during the different phases of SBS. During the adaptation phase, the surgical techniques entail preventive measures, conservative approaches, bowel revascularization and restoration of gastrointestinal continuity. As part of the rehabilitative efforts, bowel-lengthening operations and surgical techniques to slow the intestinal transit time should be offered to selected patients. The most commonly used bowel-lengthening operations are the Bianchi (**Figure 2A**) and serial transverse enteroplasty (STEP) (**Figure 2B**) procedures [23,24].

Prognostic factors

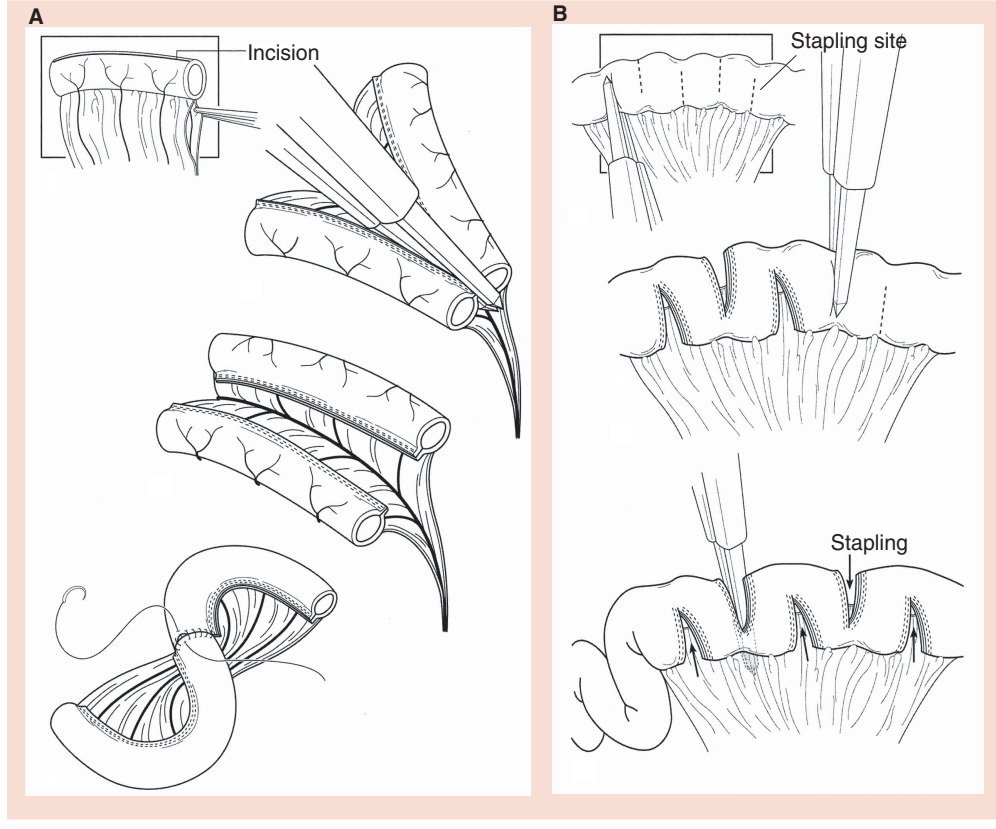
Predictors of successful rehabilitation include:

- Patient age
- Distal versus proximal resection
- Length and status of the remaining small bowel
- Presence of the ileocecal valve and or colon
- Status of the abdominal visceral vascular structures including the patency of the superior mesenteric artery and mesentericoportal circulation

Favorable prognostic factors include:

- Young age
- Healthy residual bowel with intact absorptive and motility functions
- Restored continuity of the gastrointestinal tract

Figure 2. Surgical techniques for lengthening of the intestine in patients with short bowel syndrome.



(A) Bianchi procedure. Reprinted with permission from [23]. **(B)** Serial transverse enteroplasty (STEP). Reprinted with permission from [24].

- Preservation of portion of the ileum, colon, as well as the ileocecal valve

The cumulative rehabilitative benefits of these biologic, physiologic and structural factors are determined by the ability to maximize the absorptive capacity, slow the transit time, restore the physiologic interaction between the different abdominal visceral organs and prevention of intraluminal bacterial overgrowth.

Intestinal & multivisceral transplantation

For nearly three decades, the human intestine was considered a forbidden organ for transplantation due to the associated massive lymphoid tissue (gut-associated lymphoid tissue), high antigenicity and colonization with microorganisms [25]. With the clinical introduction of the powerful immunosuppressive drug, tacrolimus (FK-506) in 1989 [26], the formidable risks of allograft rejection and subsequent lethal host infection were ameliorated and the procedure began to emerge as a rescue therapy for patients with intestinal failure who could no longer be treated with conventional modalities. However, the complexity of postoperative care and need for heavy maintenance immunosuppression, delayed the widespread use of the procedure for nearly a decade. With innovative surgical techniques, novel immunosuppressive protocols and better post-transplant management, the therapeutic indices of both the intestinal and multivisceral transplantation has significantly improved. Subsequently, the procedure has been better utilized with rewarding outcomes for patients with end-stage intestinal failure and incurable gastrointestinal diseases.

The year 2000 witnessed the US governments recognition of the procedure as the standard of care for patients with SBS and gut failure who could no longer be maintained on total parenteral nutrition (TPN) or treated with conventional therapy [27]. This milestone achievement was the result of the primary author's formal request for a national coverage policy based upon the cumulative improvement in survival and full gastrointestinal nutrition autonomy after the procedure. In its deliberation, the government considered various sources including the information submitted by this author, the 1999 technology assessment of the Blue Cross/Blue Shield Association's Technology Evaluation Center, and the report of the Center for Practice and Technology Assessment at the Agency for Healthcare Research and Quality (AHRQ).

Indications

Intestinal transplantation has been primarily utilized as a life-saving therapy for patients who have failed TPN therapy and those with life-threatening abdominal pathology. Such limited indications were implemented during the early developing phase of the procedure and continued to be used as the guidelines for clinical practice by most transplant centers, as well as healthcare providers, particularly the Center for Medicare and Medicaid Services (CMS) in the USA [27]. Failure of TPN therapy was defined by significant liver injury with elevated liver enzymes, multiple line infections, thrombosis of two or more of the central veins and frequent episodes of dehydration. However, the current substantial improvement in patient and graft survival, justifies the lifting of these restricted criteria and offering the procedure for most patients with irreversible intestinal failure.

The causes of intestinal failure differ among adults and children, with SBS being the most frequent indication for transplantation. Other indications include motility disorders, gastrointestinal neoplastic syndromes and impaired enterocyte functions. According to the Intestinal Transplant Registry (ITR) database, the most common pretransplant diagnoses are gastroschisis (21%), volvulus (17%) and necrotizing enterocolitis (12%) in children, and ischemia (23%), Crohn's disease (14%) and trauma (10%) in adults [28]. A hypercoagulable state of protein C, S and antithrombin III deficiencies, Factor V/II mutation, lupus anticoagulant and anticardiolipin antibodies are frequently diagnosed in patients with visceral vascular thrombosis. Hereditary neoplastic and motility disorders such as familial polyposis, Gardner syndrome, desmoid tumors and hollow visceral myopathy/neuropathy are not uncommon among both children and adults. Recipients with hypercoagulable syndromes must receive life-long anticoagulation therapy [29]. There have been no reported cases of primary intestinal disease recurrence, with the exception of a single case of recurrent Crohn's disease [30].

Type of intestinal transplantation

There are three main types intestinal transplantation:

- Intestine alone (**Figure 3A**)
- Liver plus intestine (**Figure 3B**)
- Multivisceral (stomach, duodenum, pancreas, intestine and liver) (**Figure 3C**)

postoperative fever, cytokine syndrome, adrenal insufficiency and histologically documented rejections. The 12 h Prograf trough levels were aimed at 10 to 15 ng/dl within the first 12 to 16 postoperative weeks. After that time, the weaning process was initiated in patients who continued to be rejection free with normal baseline endoscopic biopsy. In patients with a history of rejection, weaning was delayed for at least 8 weeks from the time of last episode. With this innovative protocol, current 1-year patient survival is 92% with a graft survival of 89%. Equally impressive is the ability to safely space the tacrolimus dose with more than half of the recipients currently on every other day (44%) or two to three single doses of tacrolimus/week (56%) with no maintenance of steroid therapy. However, rejection does occur before (first 3 postoperative months) and after weaning, with an incidence of 45%.

Infection

One of the lessons learned from the Pittsburgh early experience is the high risk of cytomegaloviral (CMV) infection and Epstein–Barr viral (EBV)-related post-transplant lymphoma [27]. Subsequently, most centers have adopted long-term prophylactic and preemptive antiviral therapy. Preemptive treatment has been guided by the recently available molecular diagnostic tests including PP65 for CMV antigenemia and quantitative polymerase chain reaction (qPCR) for EBV replication [27,36]. Such a strategy has significantly reduced the risks of CMV and EBV infections in both the adult and pediatric population, respectively [31]. The risk of bacterial and fungal infections has also been reduced by adopting perioperative prophylactic antimicrobial therapy, surveillance blood cultures and prompt removal of central lines.

Rejection

The diagnosis of early intestinal rejection remains one of the most challenging aspects of postoperative care. The early described clinical manifestations [37] and recently defined histologic criteria [38] remain the gold standard for diagnosis and treatment of rejection. Surveillance endoscopies with multiple-guided mucosal biopsies are routinely performed once or twice a week during the early postoperative period. The procedure is performed through a temporary chimney or simple loop ileostomy (**Figure 3**). Since the allograft ileum is more susceptible to rejection than the jejunum, enteroscopy with jejunal allograft biopsies is only required for cases with indeterminate ileal biopsies despite the high clinical index of suspicion. Despite all efforts, it is sometimes difficult to differentiate between allograft rejection and infection in a timely manner. The clinical availability of a reliable serum or tissue marker for prediction or early detection of rejection will undoubtedly ease and guide many aspects of postoperative management. In addition, the therapeutic indices of the procedure will continue to improve particularly the cost effectiveness and QoL.

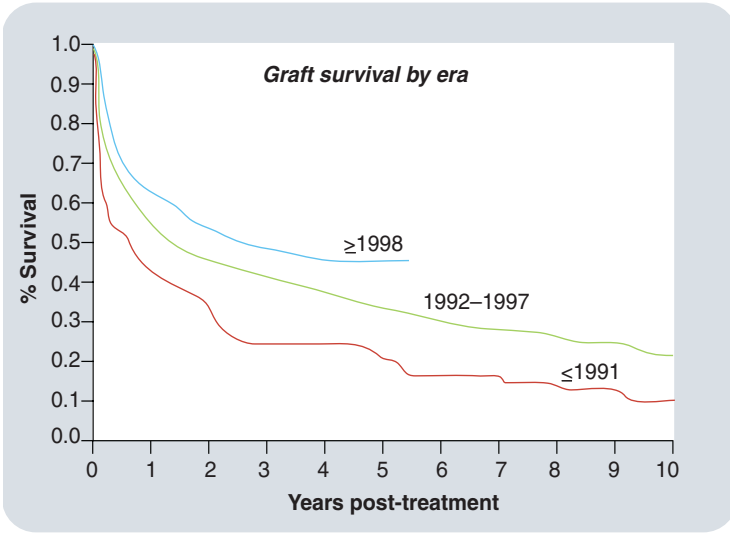
Nutrition

The nutritional care of intestinal recipients is the most complex component of the early postoperative phase. With a cumulative experience of 15 years, the current trends are early enteral feeding, utilization of nonelementary formulae and prompt discontinuation of TPN [39–41]. Contrary to early experience, most recipients receive all of their nutritional needs enterally, with complete discontinuation of TPN within the first 4 to 6 weeks after transplantation. Commonly observed postoperative self-limited gastric dysmotility has been overcome by initiation of enteral feeding through a jejunostomy tube (**Figure 3**) and use of prokinetic agents [40]. In contrast to the pediatric population, acquired eating disorders are rarely seen among adults, and discontinuation of tube feeding is commonly achieved within the first 6 to 8 weeks after transplantation. Despite discrepancies in the nutritional protocols currently adopted by the different transplant centers, early utilization of enteral feeding enhances graft adaptation, simplifies postoperative care and eliminates the potential risks associated with TPN, particularly line infections and thrombosis of the central veins.

Achievement of full nutritional autonomy is the most reliable and practical tool to assess full recovery of intestinal allograft functions. However, it is a dynamic process that is commonly triggered by multiple factors including immunologic and nonimmunologic events such as severe preservation injury, rejection, viral enteritis, life-threatening systemic infections and technically flawed operations. Accordingly, careful monitoring of the recipient's clinical and biochemic nutrition indices should guide the judicious withdrawal of TPN and advancement of the enteral feeding.

The immediate, early and long-term effects of allograft preservation injury, enteric lymphatic disruption and central denervation of the transplanted bowel, are important non-immunologic

Figure 5. The Kaplan–Meier survival curves for the intestinal transplant registry population.



Note the significant improvement in graft survival over time. Reprinted with permission from [28].

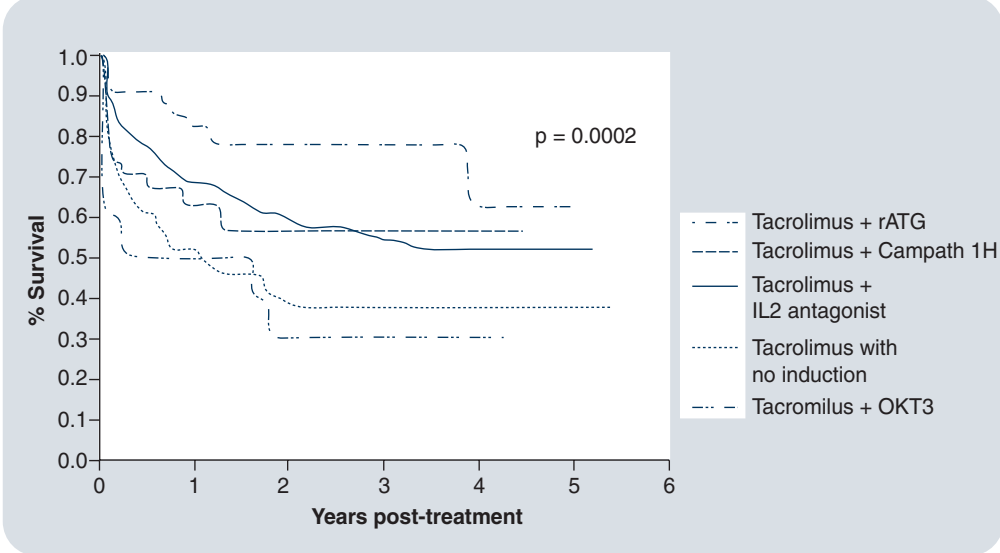
factors that contribute to delay and incomplete recovery of the intestinal graft functions. The commonly observed mutual adaptation between the engrafted viscera and residual native gut may indicate reconnection of lymphatics, reestablishment of neuroenteric functions and restoration of hormonal balance. Nonetheless, most recipients achieve long-term gastrointestinal rehabilitation with full nutritional autonomy.

Survival outcome

Current results

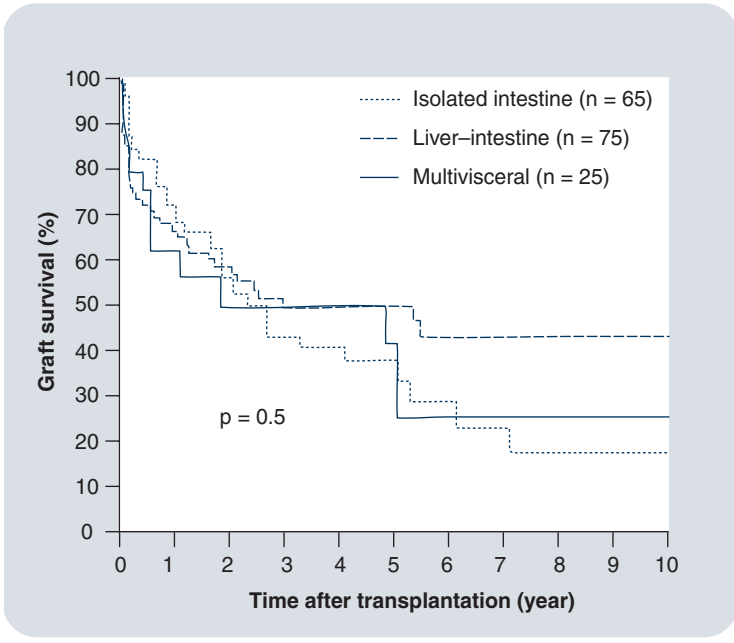
The 2003 report of the ITR highlighted a new era of intestinal transplantation with increased practicality and improved survival outcome [28]. The data confirmed the therapeutic efficacy of the procedure for the intestinal failure patients who can no longer be maintained on TPN. The analysis of 923 patients that received 989 intestinal transplantations in 19 different countries, demonstrated a continuous improvement in survival rates (**Figure 5**). Similar results have been observed with a single center experience (**Figure 4**). The 1-year survival was similar to that of liver allograft recipients. Of greater impact, were the immunosuppressive protocols that have evolved over the last 15 years with the introduction of new agents and adoption of new treatment strategies (**Figure 6**). With the current Pittsburgh recipient pretreatment protocol, the 1-year patient and graft survival was more than 90% [35]. Equally impressive is the discontinuation of TPN with achievement of full nutritional autonomy in most survivors worldwide [27,28].

Figure 6. The graft survival rates of the intestinal transplant registry population plotted according to the type of immunosuppressive protocol.



Note the significant improvement in survival with the use of induction therapy. Reprinted with permission from [28].
IL: Interleukin.

Figure 7A. Kaplan–Meier survival curves of the three different types of intestinal grafts.



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The impact of the liver allograft

The significant survival benefits of including the liver as part of the composite visceral graft, has been clearly demonstrated in two of the landmark papers in the field [31,42]. Recipients of liver plus intestine had the best long-term prognosis (**Figure 7A**) and the lowest risk of graft loss from rejection (**Figure 7B**). However, a few important points need to be addressed to put to rest current debate, particularly with recent analysis of the ITR database that included the Pittsburgh population (25–30% of the data registry). First, it is obvious from the Kaplan–Meier (cumulative) survival curves shown in **Figure 7A**, that long-term follow-up (beyond 5 years) is needed to demonstrate differences in survival in the three types of the intestinal allografts. The lower long-term survival rate of the multivisceral grafts, compared with the combined liver–intestinal grafts despite inclusion of the liver, is simply due to the documented higher risk of post-transplant lymphoproliferative disease and lethal infections among multivisceral recipients [31]. These nonimmunologic risk factors partially eroded the immunoprotective advantage of the liver and its positive impact on early and overall graft survival. To eliminate such an effect, the cumulative risk of graft loss due to rejection was calculated with and without inclusion of the liver. As shown in **Figure 7B**, the difference was highly significant (p = 0.00001), with clear documentation of the immunoprotective effect of the liver allograft.

Early transplantation

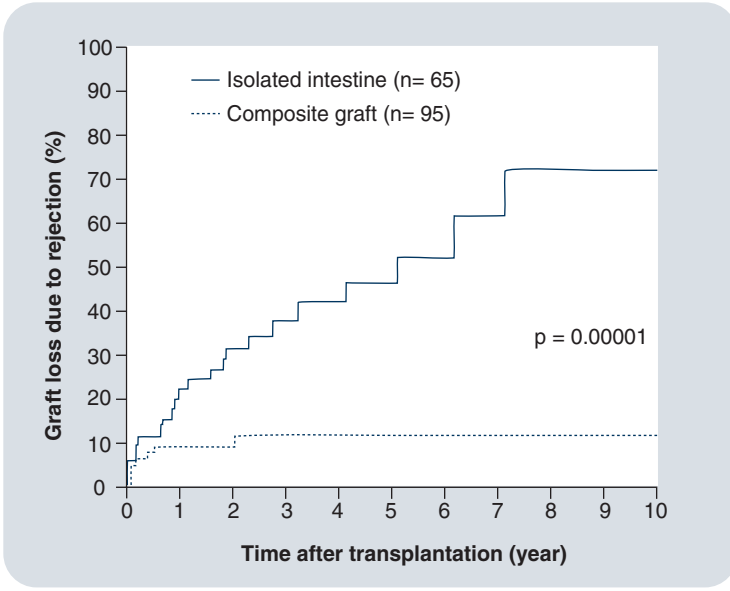
Prompt referral for transplantation has been associated with better survival outcome. Recently published data shows increased survival in patients who were waiting at home at the time of transplantation (**Figure 8**). Another potential advantage of early referral is rescuing the native liver from the deleterious effects of SBS and subsequently required TPN therapy. In addition, patients and primary caregivers are rehabilitated earlier, with a better chance of restoring the family's socioeconomic status. Equally important is the surgical option of removing the transplanted bowel, if failed, with discontinuation of immunosuppression and reinstitution of TPN.

Cost effectiveness & quality of life

With the continuous improvement in survival, the cost effectiveness and QoL issues have recently become primary rather than secondary end points. The current limitation in the availability of scientific publications that address these two important therapeutic benefits is the common use of the procedure in its three different prototypes as a rescue rather than an alternative therapy with prior exhaustion of all available conventional therapeutic modalities. Accordingly, most patients are critically ill and chronically debilitated before transplantation, with poor functional reserve.

The use of intestinal transplantation alone can be examined on a cost-effective basis due to the availability of TPN for patients with intestinal failure. In preparation for the formal request that led to government recognition of the procedure, the Pittsburgh data showed that intestinal transplantation (like kidney transplantation), becomes cost effective within the first 2 years after surgery. The cost effectiveness of a combined liver and small bowel or multivisceral transplantation is immeasurable as there is no alternative treatment. A measurable value; however, is the achievement of a high rehabilitative index in most survivors. With the continuous improvement in post-operative management and subsequent reduction in the length of the initial hospital stay as well as need for readmissions, the cost effectiveness of the procedure will continue to improve, particularly at centers of excellence [28,31].

Figure 7B. Cumulative risk of graft loss from rejection in the intestine-only and composite visceral grafts that contained liver.

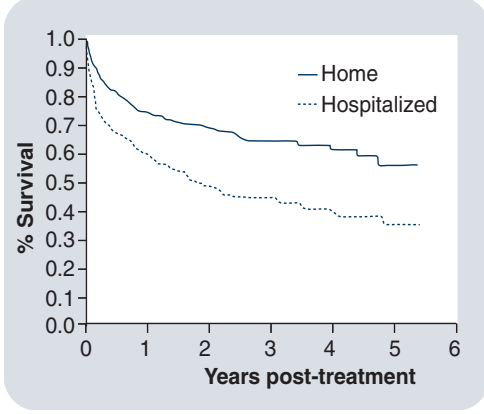


Kaplan-Meier survival curves of the three different types of intestinal grafts. Reprinted with permission from [31].

As a result of chronic illness, disease gravity and long-term use of TPN, most intestinal failure patients who undergo transplantation suffer psychiatric disorders with significant psychosocial derangement of their primary caregivers. This important observation was first reported by the London Ontario group [43] and subsequently confirmed by other centers. Accordingly, a comprehensive psychiatric assessment has been required by most centers as an essential part of the initial evaluation process.

The rich multidimensional QoL concept cannot easily be measured and properly assessed by current clinical tools, including the QoL index. Nonetheless, simple measures such as improved daily activities, personal independence, occupational rehabilitation, improved personal habits and less narcotic dependence, should be considered valuable practical tools to assess the procedure's rehabilitative index. With a lack of prospective control studies, there have been reports demonstrating significant improvement in some psychiatric domains after transition from TPN-dependence to post-transplant TPN independence [44]. These observations were validated by different centers, including reports from the ITR [28,45]. In these reports, long-term physical and psychiatric rehabilitation was achieved in 85% of the recipients who survived beyond the sixth postoperative month. Similar observations were acknowledged among the Pittsburgh 6-month survivors, with a 92% achievement of successful occupational rehabilitation [unpublished data].

Figure 8. The intestinal transplant registry patient survival according to the status at the time of transplantation.



Note a significantly higher survival rate for patients who were transplanted while waiting at home. Reprinted with permission from [28].

Establishment of an intestinal rehabilitation & transplantation center

The optimal management of patients with SBS and other gastrointestinal disorders can only be delivered through a multidisciplinary team with expertise in the medical and surgical management of these complex patients. The team must consist of a gastroenterologist, nutritionist, dietitian, pharmacist, social worker, case manager, physician assistant, clinical co-ordinator, psychiatrist, gastrointestinal pathologist and gastrointestinal surgeon. With intestinal and multivisceral transplantation being an essential part of the treatment algorithm, the rehabilitation center should be established under the umbrella of a tertiary care center, with ample experience in the field of gastrointestinal surgery and abdominal organ transplantation, particularly of the liver. The increasing practicality of the procedure compiled with cumulative improvement in survival, underscores the growing role of the local general gastroenterologists in the long-term management of these patients in collaboration with the primary tertiary center.

Highlights

- The field of short bowel syndrome and gastrointestinal failure has recently evolved particularly after the clinical introduction of intestinal and multivisceral transplantation.
- Intestinal and multivisceral transplantation has added a new dimension as a creative therapy to the short bowel syndrome patients as well as those with extensive abdominal pathology that could not be treated with conventional methods.
- Based on individual single center experience as well as the database of the intestinal transplant registry, most intestinal and multivisceral transplant survivors achieve full nutritional autonomy with excellent long term physical and psychiatric rehabilitation.
- With the current high therapeutic indices of the procedure including cost effectiveness and quality of life, we believe intestinal and multivisceral transplantation should be promptly offered to short bowel syndrome patients who fail conventional rehabilitation and those with complex abdominal pathology.

Bibliography

1. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. *JAMA* 203(10), 860–864 (1968).
2. Grant D, Wall W, Mimeault R *et al.* Successful small-bowel/liver transplantation. *Lancet* 335, 181–184 (1990).
3. Todo S, Tzakis AG, Abu-Elmagd K *et al.* Cadaveric small bowel and small bowel-liver transplantation in humans. *Transplantation* 53, 369–376 (1992).
4. Williamson RCN. Intestinal adaptation (first of two parts). Structural, functional and cytokinetic changes. *N. Engl. J. Med.* 298, 1393–1402 (1978).
5. Williamson RCN. Intestinal adaptation (second of two parts). Mechanisms of control. *N. Engl. J. Med.* 298, 1444–1450 (1978).
6. Byrne TA, Cox S, Karimbakas M *et al.* Bowel rehabilitation: an alternative to long-term parenteral nutrition and intestinal transplantation for some patients with short bowel syndrome. *Transplant. Proc.* 34, 887 (2002).
7. Jeppesen PB, Blosch CM, Lopansri JB *et al.* ALX-0600, a dipeptidyl peptidase-IV resistant glucagons-like peptide-2 (GLP-2) analog, improves intestinal function in short bowel syndrome (SBS) patients with a jejunostomy. *Gastroenterology* 122, A191 (2002).
8. Iyer, KR, Richard M. Surgery for intestinal failure. In: *Intestinal Failure and Rehabilitation: A Clinical Guide.* Matarese L, Steiger E, Seidner DL (Eds.), CRC Press, Boca Raton, London, New York, Washington D.C., 279–294 (2004).
9. Dowling RH, Booth DB. Functional compensation after small bowel resection in man. *Lancet* 2, 146–147 (1996).
10. Matarese LE, O'Keefe SJ, Kandil HM, Bond GJ, Costa G, Abu-Elmagd K. Short bowel syndrome: clinical guidelines for nutrition management. *Nutr. Clin. Pract.* 20(5), 493–502 (2005).
11. Ziegler TR, Fernandex-Estivariz C, Gu LH *et al.* Distribution of the H+/peptide transporter PepT1 in human intestine: upregulated expression in the colonic mucosa of patients with short bowel syndrome. *Am. J. Clin. Nutr.* 75, 922–930 (2002).
12. Jeppesen PB, Mortensen PB. Experimental approaches: dietary and hormone therapy. *Best Pract. Res. Clin. Gastroenterol.* 17, 1041–1054 (2003).
13. Jeppesen PB, Hartmann B, Thulesen J *et al.* Glucagon-like peptide-2 (GLP-2) improves nutrient absorption and nutritional status in short bowel patients with no colon. *Gastroenterology* 12, 806–815 (2001).
14. Byrne TA, Wilmore DW, Iyer K *et al.* Growth hormone and an optimal diet with or without glutamine reduces parenteral nutrition in patients with short bowel syndrome. *Ann. Surg.* (In press) (2005).
15. Woolf GM, Miller C, Kurian R, Jeejeebhoy KN. Diet for patients with short bowel: high fat or high carbohydrate? *Gastroenterology* 84, 823–828 (1983).
16. Nightingale JMD, Lennard-Jones JE, Gertner DJ, Wood SR, Bartran CI. Colonic preservation reduces need for parenteral therapy, increase incidence of renal stones, but does not change high prevalence of gallstones in patients with a short bowel. *Gut* 33, 1493–1497 (1992).
17. Sladen GE, Dawson AM. Inter-relationships between the absorption of glucose, sodium and water by the normal human jejunum. *Clin. Sci.* 36, 119–132 (1969).
18. Fortran JS. Stimulation of active and passive sodium absorption by sugars in the human jejunum. *J. Clin. Invest.* 55, 728–737 (1975).
19. Burnes JU, O'Keefe SJ, Fleming CR, Devine RM, Berkner S, Herrick L. Home parenteral nutrition - a 3-year analysis of clinical and laboratory monitoring. *JPEN J. Parenter. Enteral. Nutr.* 16, 327–332 (1992).
20. O'Keefe SJD, Peterson ME, Fleming CR. Octreotide as an adjunct to home parenteral nutrition in the management of permanent end-jejunostomy syndrome. *J. Parenter. Enteral. Nutr.* 18, 26–34 (1994).
21. Weinant I, Hofmann AF, Jordan A *et al.* Cholysarcosine use for bile acid replacement in short bowel syndrome. *Gastroenterology* 116, A102 (1999).
22. Kirsch M. Bacterial overgrowth. *Am. J. Gastroenterol.* 85, 231–237 (1990).
23. Bianchi A. Intestinal loop lengthening – a technique for increasing small intestinal length. *J. Pediatr. Surg.* 15, 145–151 (1980).
24. Kim H, Fauza D, Garza J, Oh J-T, Nurko S, Jaksic T. Serial transverse enteroplasty (STEP): a novel bowel lengthening procedure. *J. Pediatr. Surg.* 38, 425–429 (2003).
25. Abu-Elmagd K. The history of intestinal transplantation. In: *The History of Organ and Cell Transplantation.* Hakim NS, Papalois VE (Eds.), Imperial College Press, London, UK, 171–193 (2003).
26. Starzl TE, Todo S, Fung J, Demetria AJ, Venkataramman R, Jain A. FK 506 for human liver, kidney and pancreas transplantation. *Lancet* 2(8670), 1000–1004 (1989).
27. Abu-Elmagd KM, Bond G, Reyes J, Fung J. Intestinal transplantation: a coming of age. *Adv. Surg.* 6, 65–101 (2002).
28. Grant D, Abu-Elmagd K, Reyes J *et al.* 2003 report of the intestine transplant registry: a new era has dawned. *Ann. Surg.* 241(4), 607–613 (2005).
29. Giraldo M, Martin D, Colangelo J *et al.* Intestinal transplantation for patients with short gut syndrome and hypercoagulable states. *Transplant. Proc.* 32, 1223–1224 (2000).
30. Sustento-Reodica N, Ruiz P, Rogers A, Viciana AL, Conn HO, Tzakis AG. Recurrent Crohn's disease in transplanted bowel. *Lancet* 349(9053), 688–91 (1997).

31. Abu-Elmagd K, Reyes J, Bond G *et al.* Clinical intestinal transplantation: a decade of a single center experience. *Ann Surg.* 234(3), 404–417 (2001).
32. Murase N, Starzl TE, Tanabe M *et al.* Variable chimerism, graft versus host disease, and tolerance after different kinds of cell and whole organ transplantation from Lewis to Brown-Norway rats. *Transplantation* 60, 158–171 (1995).
33. Murase N, Ye Q, Nalesnik MA *et al.* Immunomodulation for intestinal transplantation by allograft irradiation, adjunct donor bone marrow infusion, or both. *Transplantation* 70, 1632–1641 (2000).
34. Starzl TE, Zinkemagel R. Transplantation tolerance from a historical perspective. *Nature Rev. Immunol.* 1, 233–239 (2001).
35. Starzl TE, Murase N, Abu-Elmagd K *et al.* Tolerogenic immunosuppression for organ transplantation. *Lancet* 361(9368), 1502–1510 (2003).
36. Green M, Bueno J, Rowe D *et al.* Predictive negative value of persistent low EBV viral load after intestinal transplantation in children. *Transplantation* 70(4), 593–596 (2000).
37. Abu-Elmagd KM, Tzakis A, Todo S *et al.* Monitoring and treatment of intestinal allograft rejection in humans. *Transplant. Proc.* 25, 1202–1203 (1993).
38. Wu T, Abu-Elmagd K, Bond G, Nalesnik M, Radhawa P, Demetria AJ. A schema for histological grading of allograft small intestine acute rejection. *Transplantation* 75(8), 1251–1258 (2003).
39. Reyes J, Tzakis AG, Todo S *et al.* Nutritional management of intestinal transplant. *Transplant. Proc.* 25(1), 1200–1201 (1993).
40. Abu-Elmagd K, Todo S, Tzakis A *et al.* Three years clinical experience with intestinal transplantation. *J. Am. Coll. Surg.* 179, 385–400 (1994).
41. Rovera G, Schoen R, Goldbach B *et al.* Intestinal and multivisceral transplantation: dynamics of nutritional management and functional autonomy. *J. Parenter. Enteral. Nutr.* 27(4), 252–259 (2003).
42. Abu-Elmagd K, Reyes J, Todo S *et al.* Clinical intestinal transplantation: new perspectives and immunologic considerations. *J. Am. Coll. Surg.* 186, 512–527 (1998).
43. Sten PG, Lammena P, Hould L, Grant D. Psychiatric, psychosocial and ethical aspects of small bowel transplantation. *Transplant. Proc.* 24, 1251–1252 (1992).
44. DiMartini A, Rovera GM, Graham TO *et al.* Quality of life after intestinal transplantation and among home parenteral nutrition patients. *J. Parenter. Enteral. Nutr.* 22(6), 357–362 (1998).
45. Grant D. Intestinal transplantation: 1997 report of the international registry. *Transplantation* 67, 1061–1064 (1999).

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