Robert E. Gross Lecture

Intestinal Transplantation: An Unexpected Journey

Jorge D. Reyes

Transplant Services, Seattle Children’s Hospital, Seattle, WA 98105, USA

ABSTRACT

The development of pediatric intestine transplantation has required continuous refinements in the management of intestinal failure, surgical technique, and perioperative care. 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 have resulted in better long-term survival. Paralleling this, advancements in the organ procurement techniques and organ preservation solutions have made possible the procurement and transplantation of various types of intestine containing grafts tailored to the needs of the various indications for which intestine transplantation is being performed. With improved outcomes, the indications for intestine transplantation have been better defined in the context of risk benefit for the most important complications of TPN, which include liver disease, life threatening infection, and loss of central venous access. The first survivors of transplantation would also go on to demonstrate the interaction (host-versus-graft and graft-versus-host) between recipient and donor immunocytes (brought with the allograft), which under the cover of immunosuppression allows varying degrees of graft acceptance. The struggle to achieve better transplantation survival outcomes came about with the development of improved strategies to better manage intestinal failure. This has been accomplished largely through the establishment of centers that incorporate a multidisciplinary team approach to medical and surgical care. Intestine transplantation represents a lifesaving therapy for many patients with intestinal failure who have significant complications of their disease. It is hoped that with the minimization of immunosuppression strategies currently used, the long-term survival of these intestine organ transplant recipients will continue improving, together with their rehabilitation and quality-of-life.

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1. Historical background

The evolution of clinical transplantation has spanned over 60 years and resulted in successful engraftment of kidney, pancreas, liver, heart, lung, and more recently the intestine [1]. Each organ specific trial has been able to breach the immunologic barrier using treatment strategies that seemed to be applicable to all organs. The feasibility of such management, however, is better understood in the context of shared immunologic principles. The development of these principles would begin after a series of experiments conducted between 1944 and 1960 by Medawar (Nobel Laureate, 1960) demonstrating that rejection of tissue grafts was an "immunologic event" [2]. Strategies to alter this immunologic response were described by Bellingham et al. in 1953 as "acquired tolerance" [3]; their experimental model used immunocompetent adult spleen cell injections in utero or perinatally into mice not yet able to reject them, with the consequent development of leukocyte chimerism and failure to recognize donor tissue as alien. Main and Prehn had demonstrated a similar tolerance outcome with irradiated cytolyzed mice and reconstitution with donor bone marrow [4]. This strategy was later extended to clinical bone marrow transplantation inducing stable chimerism in humans by the infusion of donor bone marrow, but in the setting of a good Human Leukocyte Antigen (HLA) match [5–7]. With successful engraftment chronic immunosuppression was frequently not needed, though there would be the risk of graft-versus-host disease (GVHD).

Whole organ transplantation was being accomplished through trial and error, without dependence on HLA matching, risk of GVHD, or leukocyte chimerism, but maintenance immunosuppression of the
recipient was necessary lifelong. Total body irradiation and the use of myeloablative drugs (6-mercaptopurine, azathioprine) had poor clinical results at first [7-9]. The development of "drug cocktails" in 1962 combined azathioprine with prednisone [10] with a success rate that allowed for further developments, which included antilymphocytic globulin, cyclosporine, and then FK506 (tacrolimus) [11,12]. These strategies controlled, to some extent, a unidirectional reaction of recipient immune cells resulting in "rejection" (the one way paradigm), which when present could be reversed with steroid therapy [13]; notable as well was the observation the maintenance immunosuppression could later be decreased over time.

Intestinal transplantation did not fit the one-way paradigm described for other organs and experimentally tested in dogs by Lillehei in 1959 and Starzl in 1960 [14,15]. Though these studies served as technical centerpieces for all intra-abdominal organ transplant procedures, the predicted cellular events of rejection and GVHD were poorly understood. As a result the early experience of intestine transplantation with and without cyclosporine was largely unsuccessful [16]; until 1990, only the isolated intestine recipient of Goulet and a living related donor intestine of Deltz had survived [17,18]. The introduction of tacrolimus in 1990 significantly improved survival, though the post-operative course remained complex and the long-term outcomes were unsatisfactory [19]. Notable in these cases was that the liver seemed protective of the intestine against rejection, as had been suggested by previous combinations of liver plus other organs such as the kidney. More importantly, the first survivors of intestine transplantation would demonstrate the interaction (host versus graft and graft versus host) between recipient and donor immunocytes (brought with the allograft); the two way paradigm [20].

2. Intestinal failure and the need for intravenous therapy or transplantation

Intestinal failure (IF) describes the inability to maintain nutritional autonomy (protein/calorie, fluid, electrolyte, micronutrients) due to loss or dysfunction of the patients native intestine, with the consequent need for permanent total parenteral nutrition (TPN). The majority of these patients have short gut as a result of congenital deficiency or acquired condition. In others, the cause of IF is a functional disorder of motility or absorption, and rarely tumor or autoimmune diseases (Table 1). Transplantation for this type of organ failure came on the heels of the successful introduction of maintenance therapy with TPN by Dudrick in the late 1960’s [21]. The success of TPN management, however, hinges around the patients’ ability to adapt in the absence of TPN induced complications.

The complications of IF can be better appreciated as syndromic and include loss of venous access, life-threatening infections, and TPN-induced cholestatic liver disease. Patients who develop these complications have a ~ 70% 1 year mortality and thus require organ replacement therapy with intestinal transplantation.

There are only 6 readily accessible venous sites (bilateral internal jugulars, subclavians, and iliac veins) for centrally placed venous catheters. Loss of venous access occurs in the setting of recurrent catheter sepsis and thrombosis; an arbitrary assumption has been that the loss of half of these sites warrants consideration for intestinal transplantation. Life-threatening catheter sepsis can result in metastatic infectious foci in lungs, kidneys, liver, and brain, the presence of unusual pathogens, and multisystem organ failure.

Cholestatic liver disease is by far the most serious complication of TPN, and may be a consequence of the toxic drug effects of TPN on hepatocytes, a disruption of bile flow and bile acid metabolism, bacterial translocation with sepsis, and endotoxin release into the portal circulation [22]. This complication varies in frequency depending on age and the etiology of the IF and is most common in neonates with extreme short gut. The effects on the liver include fatty transformation, steatohepatitis and necrosis, fibrosis, and then cholestasis. The development of jaundice and thrombocytopenia are significant risk factors for poor outcome, given the association of these changes with the presence of portal hypertensive gastroenteropathy, hypersplenism, coagulopathy, and uncontrollable bleeding [23].

3. The Transplant Operation

Intestinal grafts are usually procured from hemodynamically stable, ABO-identical brain-dead donors; as with other types of abdominal grafts, the HLA has been random and crossmatch results are usually not factored into the utilization criteria. Exclusion criteria includes a history of malignancy and intra-abdominal evidence of infection, or evidence of bowel ischemia at the time of procurement; evidence of bacterial infections is not exclusionary. Donor preparation has been limited to the administration of systemic and enteral antibiotics, and graft pretreatment using irradiation or a monoclonal antilymphocyte antibody for the prevention of GVHD has been limited to isolated centers or clinical trials; grafts have been preserved with the University of Wisconsin solution [24].

4. Types of Intestinal Grafts

The complex multivisceral grafts reported by Starzl in the first survivors of intestinal transplantation included the liver/stomach/duodenum/pancreas and small bowel [25]; this transitioned to a graft which included the liver and small bowel, and was reported by Grant et al. with some success under cyclosporine immunosuppression [26].

It became evident from these reports that intestine containing grafts could be modified to fit the requirements of the various clinical circumstances presented by patients who have IF, with or without the need for replacement of the liver. Thus, an intestine graft can be transplanted alone (as an isolated intestine graft), or with the liver/duodenum/pancreas (essentially a liver-intestine graft); the inclusion of duodenum/pancreas is an expedient way of preserving the hepatic hilus and biliary tree, thus obviating the need for biliary reconstructive procedures and facilitating both the donor and recipient operations [27].

When the recipient operation requires exenteration and replacement of all of the patient’s gastrointestinal tract (as with intestinal pseudo-obstruction or extensive Hirschsprung’s disease) and liver, then this replacement operation is known as a multivisceral transplant; in some occasions of preserved native liver function, the replacement graft will not include the liver.

The procurement and transplant of these various types of grafts rely on the preservation of the arterial vessels of celiac and/or superior mesenteric arteries, and venous outflow of superior mesenteric vein or hepatic veins. The larger liver containing grafts retain the celiac and superior mesenteric arteries; the isolated intestine graft retains the superior mesenteric artery and vein. These grafts are dissected out in situ and then removed after cardiac arrest of the donor, with core
cooling and infusion of preservation solution into the graft via the infrarenal aorta (Fig. 1).

Other modifications to these grafts have also included:

• The inclusion of colon in order to enhance independence from parenteral fluid support in the recipient, and also as an adjunct to reconstructive procedures of the ano-rectum; though the early experience with this segment was fraught with infectious complications the more recent clinical cases suggest otherwise.

• The reduction of the liver graft (into left or right side) and variable reductions of the intestine graft have facilitated abdominal closures where a larger donor than the recipient was used, given also that the recipient may have lost his or her "abdominal domain" as a consequence to short gut [28].

• The loss of abdominal domain has also prompted important innovations in the area of transplantation of abdominal wall (a composite tissue graft) or other non-vascularized components of abdominal fascia [29,30].

• The development of living donor intestine grafts has been limited, and included the isolated intestine graft as well as the combination with left lateral liver segment (from the same donor) [31].

5. The Recipient Operation

Intestinal transplantation can be a formidable technical challenge, particularly in the setting of advanced liver failure and multiple prior operations. With isolated intestinal transplantation exposure of the infrarenal aorta and vena cava allows for placement of vascular homografts using donor iliac artery and vein. The use of the native superior mesenteric vessels is also feasible (Fig. 1).

The transplantation of a liver/intestine grafts requires the removal and replacement of the native liver and, in the case of multivisceral transplantation, complete abdominal exenteration. The infrarenal aorta is exposed for placement of an arterial conduit graft of donor thoracic aorta; the venous drainage occurs through the graft hepatic drains to recipient vena cava. Intestinal anastomosis to native proximal and distal bowel is performed leaving an enterostomy of distal allograft ileum for graft surveillance.

6. The evolution of Immunosuppression

Since the early 1990’s successful immunosuppression of intestinal grafts has been based on tacrolimus and corticosteroids. The therapeutic range of tacrolimus was generally nephrotoxic, rejection rates were high (in the order of >80%), and infections with Cytomegalovirus (CMV), Epstein Barr Virus (EBV, and Post Transplant Lymphoproliferative disease [PTLD]), and other agents would result in a gradual loss of patients and grafts [19]. Subsequent protocols added drugs such as azathioprine, cyclophosphamide, mycophenolate mofetil, rapamycin, and induction with an interleukin-2 (IL-2) antibody antagonist with improvements in the incidence of rejection, yet these patients continued to require high levels of immunosuppression long term; a persistence of significant infection and toxicity continued to result in patient and graft loss. The ability to diagnose and preemptively treat CMV and EBV similarly provided an added benefit to many patients, but without significant improvements in long term survival (Fig. 2).

The intestine graft was more susceptible to rejection than other abdominal organs, and similar to other tissues exposed to environmental antigens such as skin and lung. The immunogenicity of the intestine graft could be associated with the innate immunity of the enterocyte (an antigen presenting cell) and intestinal passenger...
leukocytes (intraepithelial lymphocytes, mesenteric lymph nodes, Peyer’s patches) known to be less tolerogenic than from other abdominal organs [32]. These represent a variety of cellular, humoral, and effector mechanisms which include γ/δ T cells, phagocytic cells, NK cells, natural antibodies, compliment system, and antimicrobial peptides. Immune recognition is provided through pathogen-associated molecular patterns (PAMP), the signal transduction of which is mediated by Toll-like receptors. Intestinal transplantation is associated with inflammatory signals as a consequence to ischemia reperfusion injury, bacterial signals, and Lipopolysaccharide (LPS) translocation, recognition by the enterocyte, and subsequent activation of the effector T cell [33]. The assumption that control of such an immunologic repertoire using the strategies previously reported would result in improved survival had not been observed. The paradox could be explained by the understanding of tolerance induction and activation-induced cell death, with the development of regulatory T cells as a consequence to signaling by Th 1 cytokines. Indeed, the heavy burden of non-specific immunosuppression with steroids and calcineurin inhibitors has been shown to break tolerance and trigger rejection in various experimental models and the clinic [34,35]. The introduction in 2000 of recipient pretreatment using antilymphocyte antibodies and the elimination of recipient therapy with steroids envisaged ameliorating the ischemia reperfusion phenomenon and facilitating activation induced apoptosis (clonal deletion) [36]; this has resulted in improved transplant survival, with a significant decrease in incidence of rejection and infection, permitting the gradual decrease of immunosuppressive drug therapy within 3 months of transplant and a decline in drug toxicity events (Fig. 3).

7. The legacy of Intestinal Rehabilitation

The initial successes of intestinal transplantation in the early 1990’s resulted in an overwhelming flow of children with intestinal failure to centers performing these procedures, and though the early survival provided the encouragement for future milestones, the failure rate of patients waiting for transplant and the clinical presentation of patients who lost their grafts followed their pre-transplant cohorts. Indeed, the survival of children with IF who presented with liver disease was no greater than 30% at one year.

This prompted an important development in the management of these patients both before and after transplantation, which focused the care of the patient in the center of a multidisciplinary team of gastroenterology, surgery, nutrition, specialized nursing, interventional radiology, psychiatry, and intensive care, and with the following principles of care:

- Maintain nutrition and growth
- Optimize bowel function
- Prevent complications
- Manage complications
- Feeding therapy
- Health surveillance, immunizations, development monitoring
- Coordination of care regarding co-morbidities
- Family support

This approach would eventually result in comprehensive diagnostic evaluations, nutritional support and then rehabilitation; the incorporation of restorative surgical interventions and consideration for transplantation would be done in carefully selected patients. Surprisingly, it became evident that many patients referred for transplantation were becoming independent of TPN support, and the patients transplanted were in much better clinical condition at the time of surgery. Examples of clinical and surgical milestones which contributed to the success of these efforts included the application of ethanol lock therapy, novel lipid management strategies with consequent improvement in TPN induced liver disease, and corrective surgical procedures such as STEP [37–39].

In order to better understand and share these insights in care the Pediatric Intestinal Failure Consortium was developed, with findings delineating the standards of care which have resulted in a significant decrease in the incidence of liver disease, infection, and need for transplantation (and a decrease in death on the transplant wait list) [40].

In our efforts to improve transplant outcomes, the development of intestinal rehabilitation has demonstrated that most patients can be rehabilitated without the need for transplantation. Thus Parenteral Nutrition provided by an expert center remains the preferred treatment for chronic intestinal failure.

8. Outcomes

Intestinal transplantation is lifesaving in children with IF who have significant complications of total parenteral nutrition. Data from the International Intestinal Transplant Registry thru 2010, the OPTN/SRTR Annual Report 2012, and center-specific data reports have documented significant improvements with short- and long-term survivals for transplantations occurring principally in the last 10 years [41,42]. Over 2600 Intestinal transplants have been performed in almost 80 centers worldwide, though most cases have been done in 35 centers. Given the success of intestinal rehabilitation, however, the number of
patients needing transplantation has declined since 2005, with the majority of patients coming from home at the time of their transplant (illness severity has decreased), and over half of patients requiring only the isolated intestine transplant (through prevention/resolution of TPN induced liver disease) (Fig. 4). With the immunosuppression minimization strategies currently in use there has been a significant improvement in long-term survival as well, similar to what has been observed with other organ transplants (Fig. 5). The best survival is

<table>
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<th>Year</th>
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<td>264</td>
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<tr>
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<td>237</td>
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<tr>
<td>Pts removed during year</td>
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Fig. 4. OPTN/SRTR 2011 Annual Report demonstrating the decreasing numbers of patients listed and transplanted. http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx.

Fig. 5. OPTN/SRTR 2011 Annual Report demonstrating a significant decrease in graft failure, with an increased use of T-cell depleting agents. http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx.
achieved when the patient is at home waiting, and a liver component is added to the intestine graft.

Though the long term data are not robust, there is evidence that recipients are independent of TPN, there are good growth and development in children, and the quality of life after transplantation appears equal to or better than the quality of life on TPN [43]. The most frequent associated morbidities have been dysmotility of the graft, hypertension, osteoporosis, diabetes mellitus, and renal failure [44].

The success of intestinal transplantation has fostered the development of multidisciplinary intestinal centers which have focused on intestinal rehabilitation and improving the devastating effects of TPN on the liver. Intestine transplantation has thus become a less frequent necessity, and follows the guidelines stipulated in this report, and by others.

References