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Intestinal Transplantation: An Unexpected Journey

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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.

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 cytoablated 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

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recipient was necessary lifelong. Total body irradiation and the use of myelotoxic 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 antilymphocyte 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.

Table 1
Causes of intestinal failure in children requiring transplantation.

Short Bowel		
Congenital disorders	Volvulus	Gastroschisis
Necrotizing enterocolitus	Intestinal atresia	Trauma
Intestinal Dysmotility		
Intestinal pseudo-obstruction	Intestinal agangliosis	(*Hirschsprung disease*)
Enterocyte Dysfunction		
Microvillus inclusion disease	Tufting enteropathy	Autoimmune disorders
Crohn's disease		
Tumors		
Familial polyposis	Inflammatory pseudotumor	

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 expeditious 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 Hirschprung'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