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Mini Review

# Trends in Intestinal Transplantation

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## Introduction

Intestinal failure (IF) is a life threatening clinical problem that has been successfully mitigated withthe development of parenteral nutrition(PN). Administration of PN is not without consequences; in particular PN related liver disease (PNALD) and complications of vascular access pose severe limitation to long-termsurvival on PN. Intestinal transplantation (ITx) as a potential treatment for IF was first performed over 5 decades ago. Transplantation of the small intestine has been characterized by a severe propensity to rejection related to the immune cell mass that resides in the small bowel and therefore requirement for the most potent immunosuppression. It follows therefore that consistent success in lTx graft survival has only been possible over the last two decades, with the introduction of tacrolimus. The major unfortunate consequencesof potent immunosuppression areopportunistic infections and that include the potential to develop Epstein Barr Virus related post-transplant lymphoproliferative disease and graft versus host disease. With greater vigilance and judicious use of immunosuppression and prophylactic anti-viral medication ITx has become standard of care treatment for complications of IF. During the last two decades there have been further developments in the characteristics of the graft used, the waiting list and the outcomes of ITx.

### Composition of Multi-organ Transplant Grafts

Intestinal transplant grafts are characterized as an isolated small intestine graft, a combined liver and small intestine (L-I) graft ora multivisceral (MV) graft. The liver is included where there is significant liver fibrosis to constitute portal hypertension typically sequela of chronic use of PN particularly in infants (see below). The MV graft includes the stomach and may or may not otherwise include a liver. The MV graft is important for neuromuscular intestinal disorders that result in pseudo-obstruction and include pathology in the stomach. Apart from the isolated intestine graft the pancreas is usually included inorder to technically facilitate the transplanted graft and avoid multiple anastomoses. While these graft classifications have remained the same more recent modification of this process has included the addition of the anterior abdominal wall to facilitate closure of the abdomen where there has been a loss of the abdominal wall and abdominal domain; particularly relevant for some groups of adult patients. Another development that is perhaps a more natural evolution of the transplantation of the small intestine and that is now routine in our practice is the inclusion of the colon as part of the small intestinal graft in certain groups of patients. We consider it in all patients with very small colon remnants and therefore without an ileocecal valve and in patients with neuromuscular etiology that almost always affects the distal alimentary tract. In this latter group the graft colon allows the potential for some anatomical normalcy in the form of a pull through procedure. In patientswith short bowel syndrome and a small colon remnant there is potential for chronic diarrhea. Our experience has also been that the absence of an ileocecal valve results in ileal ulcerations from microbial ascension and by extension bacterial overgrowth. The addition of a colon graft has improved both these complications in our population.

### The Waiting List

Cadaveric grafts make up the majority of solid organ transplants and the unpredictable nature of organ availability and a short fall in available organs has given rise to waiting lists that allow hierarchical selection of recipients for transplantation. Historically mortality on the waiting list has been highest for patients awaiting an intestinal graft (1). Of all patientswith IF infants with an extremely short smallintestine have had thegreatest risk for development of progressive PNALD leading to end-stage liver disease. It follows that patientslisted for a combined liver-intestine transplant (L-ITx) has the highest mortality of all on the waiting list. We have recently shown that there has been a peak in the number of infants being listed for L-ITx around the year 2006 and the peak is preceded by a peak in waiting

listdeaths between 2002 and 2004[1]. There were no corresponding changes noted in patients listed for isolated ITx in adults or children. The ability to wean patients from PN is the key to management of IF related to a short small intestine. In our estimation our findings are an indication of the bettermanagement of IF in infants and in particularPNALD. A postponement to the development of liver disease allows more time for the small intestine to undergo adaptation and as a result the potential to wean from PN. Limiting the use of soy based lipidemulsions and or switching to a fish-oil based solution aswell as the routine use of the serial transverse enteroplasty(STEP) procedure are the best known strategies to have become popular during this time[1]. The impact of the glucagon like polypeptide-2 (GLP2)analogue teduglutide (Gattex®, NPS pharmaceuticals) in adult patients over the past few years has yet to be determined.Ultimately, this would represent a paradigm shift if it were to be effective in weaning patients from PN.

**Transplant Outcomes**

We have previously shown that patients undergoing L-ITx have a much poorer early outcome in comparison to isolated ITx (2). The poor outcome is the result of L-ITx waiting list patients being in relatively poor condition due to liver failure in the immediate pre-transplant period.Not surprisingly as noted above this is the same group of patients that has the greatest mortality on the waiting list. These pre- and post-transplant observations have led to some prioritization of organs for these patients in the last decade in the united network of organ sharing (UNOS) system in the United States. In contrast to early post- ITx outcomes after accounting for attrition from early post-transplant deaths the long-term outcome appears to be better in patients with a liver inclusive intestinal graft[2,3]. We have also previously demonstrated that a liver inclusive graft may confer a benefit to other solid organ transplants including lung transplants[4]. This implies that rather than a physiologic or anatomical benefit to the small intestine the liver may confer an immunologic change towards greater tolerance of other organs transplanted simultaneously with the liver. More recent data indicate that there has been an improvement in the early survival of this group of patientswith one year survival now equivalent to patients undergoing an isolated ITx. It is well known that the intestine has a large immune mass that is a necessary part of enteric sampling of exogenous antigens and developing tolerance during early childhood. And that processing of antigens is a critical event that occurs in the liver through the portal circulation. It has also been reported in pediatric patients that food allergy may be increased after solid organ transplantation. While there are reports in other organ solid organ transplant groups the greatest number of publications has been from liver transplant populations with the implication that immune dysregulation with tendency towards a T-helper cell 2 response may be the mechanism[5]. We have recently described an increase in prevalence of food allergy in children after ITx similar to liver pediatric liver transplant patients[5]. We postulate that immune dysregulation in the liver in addition to abnormal uptake of food proteins by the transplanted intestine may be cumulative in development of food allergy in patients after ITx.

In summary ITx is now an established standard for patients with IF who develop complications on PN. There continue to be developments in the care of patients with IF and post-transplant outcomes leading to an improved outlook for this patient group.

**Conflict of Interest:** none

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