Trends in Intestinal Transplantation

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Introduction

Intestinal failure (IF) is a life threatening clinical problem that has been successfully mitigated with the 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-term survival 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 ITx graft survival has only been possible over the last two decades, with the introduction of tacrolimus. The major unfortunate consequences of potent immunosuppression are opportunistic 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 or a 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 patients with 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 patients with IF infants with an extremely short small intestine have had the greatest risk for development of progressive PNALD leading to end-stage liver disease. It follows that patient listed 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 correspond-
ing changes noted in patients listed for isolated ITx in adults or
children. The ability to wean patients from PN is the key to man-
agement of IF related to a short small intestine. In our estimation
our findings are an indication of the better management of IF in
infants and in particular PNALD. A postponement to the develop-
ment 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 lipids and or switching
to a fish oil based solution as well as the routine use of the se-
rial 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
couple of years has yet to be determined. Ultimately, this would
represent a paradigm shift if it were to be effective in weaning pa-
tients from PN.

**Transplant Outcomes**

We have previously shown that patients undergoing
L-ITx have a much poorer early outcome in comparison to iso-
lated ITx (2). The poor outcome is the result of L-ITx waiting
list patients being in a 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 mor-
tality on the waiting list. These pre- and post-transplant observa-
tions 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 out-
comes 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 simulta-
aneously with the liver. More recent data indicate that there has
been an improvement in the early survival of this group of pa-
tients with one year survival now equivalent to patients under-
going 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 oth-
er 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 pa-
tients\([5]\). 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 pa-
tients with IF who develop complications on PN. There continue
to be developments in the care of patients with IF and post-trans-
plant outcomes leading to an improved outlook for this patient

group.

**Conflict of Interest:** none

**References**

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