Intestinal and Multivisceral Transplantation

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University of Pittsburgh, Pittsburgh, PA.
Summary

- History and its lessons
- Intestine transplantation at Pittsburgh
- Intestine transplantation worldwide
- What is new
T.E. Starzl, H.A. Kaupp Jr

1960: Mass homotransplantation of abdominal organs in dogs

Transplantation of Multiple Abdominal Viscera

Thomas E. Starzl, MD, PhD; Marc I. Rowe, MD; Satoru Todo, MD; Ronald Jaffe, MB, BCh;
Andreas Tzakis, MD; Allen L. Hoffman, MD; Carlos Esquivel, MD, PhD; Kendrick A. Porter, MD, DSc;
Raman Venkataramanan, PhD; Leonard Makowka, MD, PhD; Rene Duquesnoy, PhD

(JAMA. 1989;261:1449-1457)

(JAMA. 1989;261:1458-1462)
Small Bowel and Liver/Small Bowel Transplantation in Children

1993

Jorge Reyes, Andreas G. Tzakis, Satoru Todo, Bakr Nour, and Thomas E. Starzl
Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh; and the Veterans Administration Medical Medical Center, Pittsburgh, PA

N=11
M:F 4:7
0.5-10.2 years
L-ITx: ITx 8:3
Alive 8, off TPN
Dead: 3, GVHD, PTLD, Bile leak
1990-1995

- N=71 grafts in 67 recipients, 63 with one year follow-up
- 28 functioning grafts, 4 on TPN after enterectomy
- 35 graft losses-technical 10, rejection-6, infection-19
- Infection: Lymphoma-8, CMV-5, bacterial-6
- Contributors to graft loss: rejection, OKT3, steroid use, high FK levels, graft colon, CMV+ donor

Results
Of the first 63 recipients, 32 are alive: 28 have functioning primary grafts and 4 have resumed total parenteral nutrition after graft enterectomy. Thirty-five primary grafts were lost to technical and difficult to pinpoint because of multiple interlocking factors (Fig. 6). The principal diagnosis was rejection in only 6 cases, whereas an infectious complication attributable to antirejection therapy was the major diagnosis in 19. The responsible microorganisms included bacteria and fungi (n = 6), but among the viruses, cytomegalovirus (CMV) alone accounted for nearly as many losses (n = 5). Moreover, Epstein–Barr virus (EBV) associated B-cell lymphomas occurred in 12 (19%) of the 63 patients, of whom 8 lost their grafts and died of this complication. Eleven of the 12 patients who developed the lymphomas had been treated with OKT3.

Retransplantation
Four patients underwent retransplantation on the same day as primary graft removal (two liver-intestine) or 1 to 2 months later (two intestine only). They died 47

Outcome Analysis of 71 Clinical Intestinal Transplantations

ative donor was used, but only 14% with a CMV-positive donor (Fig. 7). As recently reported in detail, therapy that can regularly control this infection in other kinds of allograft recipients was only marginally effective in the intestinal recipient. Once the clinical diagnosis of CMV was made, the predominant target in essentially all cases was the intestinal allograft itself. The resulting ulcerations were associated with bacterial translocation.

Inclusion of a colonic segment in 29 patients was a significant risk factor. Significantly better graft survival was observed in 34 patients without the colon than with it (Fig. 8). Although the negative colon influence was more pronounced in adults, it also was identified in the
History

- **1990**: First successful liver-small bowel Tx, Grant et al.
- **1995**: 71 consecutive intestine transplant procedures, 32 survivors, 28 off TPN, Todo and Starzl et al.
- **2001**: Medicare coverage for intestine Tx in the U.S.
- **2015**: 500 consecutive intestine transplants at Pittsburgh, Abu-Elmagd et al.
- **2016**: Intestine transplant registry reports 3174 transplants from 29 centers representing 90% of international activity.
History Lessons

• Technically feasible: limit anastomotic leaks with duodenal-sparing liver-small bowel composite graft

• Rejection, infection, lymphoma and GVHD common occurrences: avoid colon, avoid CMV+donors

• One-year survival roughly 50%

• Need for more effective less toxic immunosuppression
Intestine Transplantation today

- Multidisciplinary evaluation
- The procedure
- Expected challenges and adverse events
- Survival outcomes
- Growth
MULTIDISCIPLINARY Intestine transplant evaluation

**Does clinical need exist, If so, which operation**
- Short gut (TPN >50% calories) with complications: growth failure, liver failure, access failure
- Liver involved: biopsy, TPN cholestasis vs cirrhosis
- GI contrast studies: ? residual bowel, gut rehab procedures
- Motility studies: connect vs end-ileostomy, include stomach

**Can the recipient undergo ITx safely, and make good use of organ**
- Comorbidities: prematurity sequelae-bronchopulmonary dysplasia, irreversible CNS damage, mitochondrial disease

**Is Psychosocial support adequate to handle**
- Meds, compliance, surveillance requirements
Indications

**Adults**

- **Short Gut**: 64%
- **Ischemia**: 22%
- **Crohn's**: 11%
- **Other Short Gut**: 10%
- **Volvulus**: 7%
- **Trauma**: 6%
- **Retransplant**: 7%
- **Other**: 11%
- **Tumor**: 15%
- **Motility Disorder**: 11%
Indications

Pediatric

- Short Gut: 63%
- Gastrochisis: 22%
- Volvulus: 15%
- N. Enterocolitis: 13%
- Ischemia: 1%
- Atresia: 4%
- Other Short Gut: 4%
- Trauma: 1%
- Other: 3%
- Tumor: 1%
- Malabsorption: 9%
- Motility Disorder: 19%
- Retransplant: 8%
The multivisceral donor and Intestine grafts

Sindhi, Transplantation, 1995

Liver-intestine allograft

Isolated Intestine Allograft

+ stomach = multivisceral

+ stomach = modified multivisceral
Intestine transplantation: procedure

Mazariegos, Celik et al 2016

**Arterial conduit on Infrarenal aorta**

**SMV extension graft on infrarenal cava for Isolated intestine Tx**

**Loop ileostomy, end colostomy, G-tube, J tube**

Same for isolated and Liver-intestine Tx

Upper caval venous outflow for Liver-intestine and MVTx

Avoid J-tube if bowel caliber is small
Abdominal domain and Wound management

- Prevent abdominal compartment syndrome, silastic mesh
- Delayed closure: skin or biologic
- Avoid tension and excessive debridement

**NUTRITION**

Skin closure

Skin + biologic
Challenge: Stomas

Early
- Avulsion: Vac dressing
- Prolapse: prevention, fix mesentry, fix to peritoneal surface

Post-closure
- obstruction, recheck distal motility, reverse if needed
- Enterocutaneous fistula after closure

• NUTRITION
Challenge: Vessels

Pseudoaneurysm

- Prevention: generous bites during anastomosis, meticulous hemostasis of suture line
- Treatment: surgical if accessible, interventional radiology if intra-abdominal
Technical challenges and complications

- Abdominal compartment syndrome: delayed closure
- Bleeding
- **Volvulus:** isolated ITx, long vascular conduits to aorta and IVC, failure to fix mesentry
- **Paraplegia** (suprarenal conduit grafts)
- Pseudoaneurysm: aorto-aortic, tip of aortic conduit
- **Ureteric injury** in reTx or enterectomy or prior extensive surgery-stents
- Venous outflow stenosis-growth factor
- Stomal prolapse-fix mesentry, fix to peritoneal surface
- Enterocutaneous fistula
OVERALL PATIENT AND PRIMARY GRAFT SURVIVAL
(n=244, 2016, Soltys, Celik, Mazariegos et al, 2016)
Survival: Induction vs no induction

Seminars in Pediatric Surgery, Volume 19, Issue 1, 2010, 68–77

Combined Liver-intestine

Graft

Patient

Intestine

81% vs. 58%, \( P = 0.009 \)

76% vs. 52%, \( P = 0.008 \)

(73% vs. 48%, \( P = 0.047 \))

56% vs. 40%, \( P = \text{NS} \)

(85% vs. 56%, \( P = 0.007 \)).
Survival: Liver-containing allografts do better
Soltys, Celik, Mazariegos et al, 2016
Problem:

Immunosuppression Failure

Acute cellular Rejection (30-60%)

Normal (Rejection-free)

PTLD (10-12%)  GVHD (10-12%)

Too little – Just right

Too much – Too much

PTLD 11/103 = 11%
CMV 13/103 = 13%
GVHD 15/103 = 15%

Failure

Normal (Rejection-free)

PTLD (10-12%)  GVHD (10-12%)

Seminars in Pediatric Surgery, Volume 19, Issue 1, 2010, 68–77
Rejection

Cellular
30-60%
50% resistant
Rejection-free
12-24% at 2 to 5y

Antibody-mediated
10%

C4d
Late sequelae

Chronic rejection
- Median time: 39 months (22-67)
- ITx: Liver-intestine Tx: 8/38, 21.05% vs. 2/65, 4.6%, p=0.017

Renal Failure
- Incidence: 5/103, 4.6%
- Prior renal insufficiency: 3/5, 60%
Steroid avoidance favors growth
The state of Intestine Transplantation
Internationally

- International Transplant Registry
- 90% of active centers report to the Registry
- Survival trends are improving
- Colon increasingly included in the allograft
# Global Clinical Experience with ITx

*(All recipients transplanted between Jan 1985-Jan 2016)*

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Transplants</strong></td>
<td>3194</td>
<td>1731</td>
</tr>
<tr>
<td>Center count</td>
<td>85</td>
<td>64</td>
</tr>
<tr>
<td><strong>Active Centers</strong></td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>ITx alone</td>
<td>1429 (44.7%)</td>
<td>622 (35.9%)</td>
</tr>
<tr>
<td>Intestine+Liver</td>
<td>949 (29.7%)</td>
<td>767 (44.3%)</td>
</tr>
<tr>
<td>MVT+Modified MVT</td>
<td>656+160 (25.5%)</td>
<td>299+43 (19.8%)</td>
</tr>
<tr>
<td><strong>Current survivors</strong></td>
<td>1651</td>
<td>883</td>
</tr>
</tbody>
</table>
## Multiple Variable Regression Analysis: Preliminary Results

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Overall*</th>
<th>P value</th>
<th>1 Yr Conditional</th>
<th>p-v</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001 - 2014 Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infant (0-2 Years)</strong></td>
<td>0.84</td>
<td>0.005</td>
<td>0.71</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Pediatric (3-6 Years)</strong></td>
<td>0.75</td>
<td>0.037</td>
<td>0.79</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Regraft vs. Primary</strong></td>
<td>1.85</td>
<td>0.08</td>
<td>1.26</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Called in from home for IT</strong></td>
<td>0.55</td>
<td>0.01</td>
<td>0.87</td>
<td>0.23</td>
</tr>
<tr>
<td>+ Liver component</td>
<td>0.78</td>
<td>0.031</td>
<td>0.68</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Rapamycin Maintenance</strong></td>
<td>0.87</td>
<td>0.023</td>
<td>0.77</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Lower ratio = improved survival*
Causes of Death

- Kidney
- Liver
- CV
- Lymphoma
- Technical
- Graft
- Sepsis
Survival by era: Before and after 2000

Primary Graft Survival by ERA

- 2001-2015: 60% (N=159)
- 1990-2000: 23% (N=83)

Retransplant 5 Year Graft Survival by ERA

- 2001-2015: 79% (N=19)
- 1990-2000: 40% (N=5)
Colon Inclusion Over Time

Adding a colon segment (2001-2014):

- 3% higher rate of TPN and fluid Independence ($p = 0.031$)
- 9% superior graft survival at 3 years ($p = 0.02$)
What is New

• Inclusion of colon
• FDA-approved test to predict cellular rejection
• GVHD: failure to repopulate donor allograft mucosa
• Gut microbiome and metabolome as biomarkers
Allospecific CD154+T-cytotoxic memory cells (CD154+TcM)

- FDA-approved, August 2014

- Overnite
- Disease-specific
- Personalized
- **Rejection-risk index ≥ 1.1**

### Inflammatory response (CD154+cells)

<table>
<thead>
<tr>
<th>Organ</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>58</td>
<td>92%</td>
<td>85%</td>
<td>Am J Transplant, 2009</td>
</tr>
<tr>
<td>Intestine</td>
<td>32</td>
<td>93%</td>
<td>88%</td>
<td>Surgery, 2009</td>
</tr>
<tr>
<td>Kidney</td>
<td>43</td>
<td>88%</td>
<td>88%</td>
<td>Transplantation, 2011</td>
</tr>
</tbody>
</table>
Replacement of donor lymphoid tissue in small-bowel transplants

Prof Yuichi Iwaki, MD, PhD, Prof Thomas E. Starzl, MD, PhD, Atsuhito Yagihashi, MD, PhD, Satoshi Taniwaki, MD, Kareem Abu-Elmagd, MD, Andreas Tzakis, MD, John Fung, MD, PhD, and Satoru Todo, MD, PhD

Departments of Surgery (Prof Y. Iwaki, MD, PhD, Prof T. E. Starzl, MD, PhD, A. Yagihashi, MD, PhD, S. Taniwaki, MD, K. Abu-Elmagd, MD, A. Tzakis, MD, J. Fung, MD, PhD, S. Todo, MD, PhD) and Pathology (Y. Iwaki), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA


Non-rejector: HE x20 and FISH for XY and CD45 with 100% female (XX) population of graft
Refractory GVHD: failed repopulation of lamina propria with recipient immune cells

Allograft biopsy no ACR

Skin GVHD: Ulcerated skin, loss of keratinocytes (lower edge), adnexal gland with frequent apoptoses (black arrows)

Allograft lamina propria 97% CD45+ cells (green outline) are XY+ in girl with GVHD

Bone marrow biopsy shows 100% XX cells in girl with GVHD
The gut microbiome and metabolome


Girlanda et al. American Journal of Transplantation
doi: 10.1111/j.1600-6143.2012.04183.x
Summary

• Intestine Tx is a viable option for refractory short gut syndrome.

• Survival continues to improve, except isolated ITx with 50% median 5-year graft survival.

• Surveillance of rejection and infection has been critical.

• Cohesive team which includes intestinal rehab services.

• Complex management needs requires multidisciplinary team including interventional radiology, advanced GI imaging, pharmacology, nutritional support.

• INSTITUTIONAL SUPPORT
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- Szalay family foundation.
- Hillman Foundation of Pittsburgh
- Plexision, Pittsburgh, PA.
Summary

Viable option for refractory short gut
Survival continues to improve, except isolated ITx which lag its peers with 50% median 5-year graft survival
High incidence of rejection and complexity requires multidisciplinary team including interventional radiology, advanced GI imaging
Immunological

11/103 = 107%