Intestinal Transplantation

Cristiano Quintini, MD
Intestinal Rehabilitation and Transplant Program
Cleveland Clinic
History of Intestinal Transplantation

- Initially attempted in early 1960’s
- Only a few unsuccessful cases until the late 1980’s
- With the development of Cyclo/Tacrolimus successful transplantation has been achieved
- Guidelines for intestinal transplantation adopted by United States Department of Health and Human Services in 2000
## Intestinal Transplantation Under Cyclosporine

<table>
<thead>
<tr>
<th>Location</th>
<th>Date</th>
<th>Organ(s)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittsburgh</td>
<td>Nov ’87</td>
<td>Multivisceral</td>
<td>6.5 mos</td>
</tr>
<tr>
<td>Kiel</td>
<td>Aug ’88</td>
<td>Intestine</td>
<td>61 mos</td>
</tr>
<tr>
<td>Ontario</td>
<td>Nov ’88</td>
<td>Liver/Intestine</td>
<td>66 mos</td>
</tr>
<tr>
<td>Paris</td>
<td>Mar ’89</td>
<td>Intestine</td>
<td>still alive!</td>
</tr>
<tr>
<td>Ontario</td>
<td>Nov ’89</td>
<td>Multivisceral</td>
<td>58 mos</td>
</tr>
<tr>
<td>Innsbruck</td>
<td>Dec ’89</td>
<td>Multivisceral</td>
<td>7.5 mos</td>
</tr>
</tbody>
</table>
Causes Of Intestinal Failure

- **CHILDREN**
  - Gastrochisis
  - Necrotizing enterocolitis
  - Volvulus
  - Intestinal atresia
  - Microvillus disease
  - Pseudo-obstruction
  - Familial polyposis

- **ADULTS**
  - Vascular occlusion
  - Crohn’s disease
  - Abdominal trauma
  - Radiation enteritis
  - Surgical adhesions
  - Pseudo-obstruction
  - Desmoid tumor
Treatment Of Intestinal Failure

• Medical/Pharmacological
• Surgical restoration
• TPN
• Transplantation
Surgical Management of Short Bowel Syndrome

Strictureplasty

Reversed Segment

STEP procedure

Tapering

Valve

Lengthening
• The ‘artificial gut’ for Intestinal failure and represent the treatment of choice for irreversible CIF

• The first patient was discharged on HPN by Shils et al. in the late 1960s

• About 20–50% of patients who starts HPN has a reversible CIF and are able to stop treatment after 1–2 years

• 2-year PN represents the limit between transient and permanent intestinal failure.
HPN complications

- Line sepsis
- Venous access thrombosis
- TPN-induced liver disease
- Psychological and economic factors
31%–68% of HPN have short bowel syndrome

• Analysis on 124 consecutive adults with nonmalignant SBS enrolled from 1980 to 1992 at 2 home PN centers.

• Analyzed for survival and PN dependence probabilities
HPN
Overall survival

Messing B. et Al
Gastroenterology 1999;117:1043–1050
HPN
Primary diagnosis survival curve

Messing B. et Al
Gastroenterology 1999;117:1043–1050
HPN
Effect of remnant bowel

Messing B. et Al
Gastroenterology 1999;117:1043–1050
HPN
Colon and ICV

[Graph showing survival probability over years after bowel resection with two lines for colon in continuity and end-jejunostomy, with p < 0.01 indicated.]
HPN
Primary diagnosis survival curve
TPN - Associated Liver Disease

Complicated Liver Disease*

*Definition: extensive portal fibrosis or cirrhosis, bili $\geq 3.5\text{mg/dl}$ for $\geq 1\text{m}$, ascites, portal HTN, hepatic encephalopathy or factor $V < 50\%$

100% mortality at an average of 10.8 ± 7.1 months after the initial bilirubin elevation.
Indications for Referring Adults to Intestinal Tx Center

- Liver disease despite expert PN management
- Loss of all but 2 major venous access routes (1 should be above diaphragm)
- Recurrent or life threatening central line sepsis
- Inability to maintain hydration/nutrition with PN
- Dismotility disorders
- Need for extensive evisceration (desmoid, trauma or rare selected malignancies)

Annual Waiting List Death Rates All organs

(per 1,000 Patient-Years at Risk Waiting)

From Jonathan Fryer MD. Northwestern University September 2006
Acceptance Criteria

- Age 1 – 65
- Irreversible intestinal failure
- Failure / complication of TPN
- Early referral to avoid associated need for combined intestine & liver transplant
- No contraindication to surgery
- Patient readiness and caregiver support
Liver and intestine

Isolated Intestine

Liver, intestine and pancreas

Liver and intestine

Multivisceral
Types of Grafts in Clinical Intestinal Transplant

- Isolated bowel graft plus:
  - Stomach, duodenum and pancreas
  - Liver
  - Colon
  - Spleen
Technical data

- Operative time: 10:40 (± 2:10)
- Average Blood loss: 10-25 PRBCs
- Cold ischemia time: 6:20 (± 1:10)
Induction and Maintenance Therapy

- Steroids
- Tacrolimus
- Sirolimus
- Monoclonal Antibodies
  - Campath
  - Muromonab CD3 (OKT3)
- Polyclonal Antibodies
  - Thymoglobulin
  - ATGAM
- IL-2 Receptor Blockers
  - Daclizumab (Zenapax)
Treatment of rejection episodes

Intestinal transplant

- Mild rejection: Steroid bolus and cycle; increase in baseline immunosuppression; if no response in 2 days, OKT3 (7-14 days)

- Moderate and severe rejection:
  Thymoglobuline/Infliximab/Alefacept/
Intestinal Transplant

Abdominal Closure
Many patients undergoing intestinal or multivisceral transplantation have:

- Past history of complete midgut removal with the loss of the abdominal cavity domain

- Severely damaged abdominal wall (from repeated laparotomies, tumors, enterocutaneous fistulae)
Intestinal Transplant Program
Abdominal wall reconstruction
Difficult abdominal Closure
MESH CLOSURE
Combined intestinal and abdominal wall transplantation

Abdominal wall flap
- skin and subcutaneous tissue
- muscular fascia
- rectus abdominis muscles
- parietal peritoneum
Donor: pre-op drawing

Abdominal wall flap

Abdominal wall flap in perfusion with Celsior sol.
Immediate post-op

6 months post-op
Simultaneous or Sequential Combined Living Donor-Intestine Transplantation in Children

Giuliano Testa,1,5 Mark Holterman,2 Herand Abcarian,3 Ronak Iqbal,4 and Enrico Benedetti4

•Four pediatric recipient
  -Left lateral segment
  -Averages of 160 cm (150–180 cm) of terminal ileum
•The mother was always the donor!

The decision to proceed with a single- or a two-stage procedure was dictated by the presence of a positive cross-match and preformed antibodies against the donor in one case and by advanced end-stage liver disease in two cases.

The rationale in the latter was to re-establish quasinormal liver function before submitting the child to the intestine transplant.
Donor anatomy
Donor operation
### Living Donor Database

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of centres</td>
<td>16</td>
</tr>
<tr>
<td>Number of transplants</td>
<td>41</td>
</tr>
<tr>
<td>Current survivors</td>
<td>21</td>
</tr>
</tbody>
</table>
Intestinal Transplant Complications

Rejection
Intestinal Transplant Rejection

- Kidney: Renal failure, HD
- Pancreas: Endocrine failure/Insuline
- Liver: Increased LFTs, Liver failure (Days), Death
- Intestine: Disruption of Blood/Enteric barrier and SEPSIS
Patient Symptoms

- Symptoms are very aspecific (nausea, vomiting, increased stoma output, fever)
- Target: small intestine, distal ileum
- Liver is protective!
Rejection
Surgeon Symptoms

MILD/MODERATE
Chest pain, Nausea, Vomiting, Diarrhea

SEVERE
Fever, ST-elevation and seizures
HISTOLOGICAL ANALYSIS

- Biopsy of the affected organ is still the gold standard.
- Try to get results same day
- Experienced pathologists

- No rejection: normal tissue
- Indeterminate (Grade IND)
- Mild acute cellular rejection (Grade 1)
- Moderate acute cellular rejection (Grade 2)
- Severe acute cellular rejection (Grade 3)
ZOOM ENDOSCOPY

- Magnifies > 100 folds
- Minute analysis of mucosa
- Only in adult/older children
Endoscopy protocol

- Twice/week endoscopy in the first 4 weeks after transplant
- Once weekly for 3 months, then monthly
- Daily or every other day when rejection diagnosed until resolution of clinical and histological signs
“Endoscopy dogma”

- You are never wrong to do a scope!
- If there is something suspicious, scope!
- Scope at the drop of a hat!
- If you do not know what to do, scope first, then think about it!
- Cleveland winters are good for scopes!!
Normal mucosa
Mild rejection
Moderate rejection
Severe rejection
SEVERE REJECTION
MUCOSAL SURVEILLANCE

• ZOOM VIDEO ENDOSCOPY & INTESTINAL BIOPSY

Twice a week (up to 15 POD)
Weekly (up to 2\textsuperscript{nd} month)
Monthly or ACR suspicion

• INTRAVITAL POLARIZED LIGHT MICROSCOPE. CYTOSCAN\textsuperscript{®} (after endoscopy)
OPS IMAGING
Severe acute ACR
Currently no biochemical markers of intestinal rejection

- Citrulline is an amino-acid whose serum level is solely dependent on enterocyte metabolism
- Low levels of citrulline are seen in patients with bowel dysfunction or short gut
- Working hypothesis: could citrulline levels vary in serum of intestinal transplant patients according to graft function?
Correlation of citrulline with rejection grade

Mean + SD

<table>
<thead>
<tr>
<th>Serum Citrulline [umoles/ml]</th>
<th>Pre-Trans</th>
<th>No Rejection</th>
<th>Grade of Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19 ± 3</td>
<td>35 ± 5</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>1</td>
<td>13 ± 2</td>
<td>25 ± 3</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>2</td>
<td>9 ± 1</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>2.5 - 4.0</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
</tr>
</tbody>
</table>
Intestinal Transplant Complications

Infections
Infections

- Nearly all patients (>95%) develop one or more episodes of documented infections after transplant
- Average number of infection episodes: 5 per patient
- More common early after transplant: 50% 1-3 months, 25% 3-12 months, 25% > 12 months
- Causative agents:
  - 90% bacterial
  - 6% fungal
  - 4% viral
  - Many episodes of mixed infections (viral/bacterial or bacterial/fungal)
- Location:
  - Blood
  - Respiratory tract
  - Wound
  - Intra-abdominal
  - Urine
  - Central venous catheter
Intestinal Transplant Complications

PTLD
Post-Transplant Lymphoproliferative Disorder
Definition-Pathogenesis

- Post-transplant lymphoproliferative disorders (PTLD) are a spectrum of diseases in which there is abnormal proliferation of lymphocytes (most cases: Epstein Barr Virus-infected B-lymphocytes) in all tissues and organs where lymphocytes are presents.

- For most cases of PTLD, EBV infection of the B-cells is the first step.
## Lymphoproliferative Disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>n/N</td>
</tr>
<tr>
<td>Intestine</td>
<td>1 / 18</td>
<td>28 / 252</td>
<td>8 / 168</td>
</tr>
<tr>
<td></td>
<td>(5.6%)</td>
<td>(11.1%)</td>
<td>(4.8%)</td>
</tr>
<tr>
<td>Intestine + liver</td>
<td>1 / 13</td>
<td>41 / 278</td>
<td>7 / 99</td>
</tr>
<tr>
<td></td>
<td>(7.7%)</td>
<td>(14.7%)</td>
<td>(7.1%)</td>
</tr>
<tr>
<td>Multivisceral</td>
<td>1 / 3</td>
<td>17 / 83</td>
<td>9 / 86</td>
</tr>
<tr>
<td></td>
<td>(33.3%)</td>
<td>(20.5%)</td>
<td>(10.5%)</td>
</tr>
</tbody>
</table>
Intestinal ulcer from PTLD lesion

Microscopic appearance of intestinal PTLD
Treatment

Reduction or complete discontinuation of immunosuppression

- Antiviral medications (Gancyclovir, Acyclovir), hyper immune immunoglobulins (Cytogam)
- Anti- B cell antibody therapy (Rituximab)
- Surgical resection/local irradiation
- Interferon alpha
- Conventional chemotherapy
Intestinal Transplant Complications

GVHD
Graft Versus Host Disease
GVHD

Graft-versus-host disease (GVHD) is a rare but potentially fatal complication of solid organ transplant in which functional immune cells (mature T and B cells) in the transplanted organ recognize the recipient as "foreign" and mount an immunologic attack.
Treatment

- *Increase/decrease ISP????
- *Prognosis is POOR (70-90% death rate)
Intestine Transplant Registry

Supported by an unrestricted educational grant from Astellas, Canada, Inc.

www.IntestineTransplant.org
1. Database includes ~95% of the world experience.
2. The longest surviving recipient was transplanted 18 years ago and she still has a functioning graft!
69 Participating Programs
Ordered by Case Volume
Demographics

Gender Distribution

- Males 52%
- Females 48%

Age at Transplant

- > 50
- 18-50
- 6-18
- 2-6
- <=2
Indications in Children

- Gastrochisis: 20%
- Necrotizing Enterocolitis: 13%
- Intestinal Atresia: 8%
- Short Gut Other: 5%
- Microvillus Inclusion: 6%
- Malabsorption: 2%
- Aganglionosis/Hirschprung's: 9%
- Pseudo-Obstruction: 8%
- Other Motility: 1%
- Tumor: 1%
- Re-Tx: 8%
- Volvulus: 17%
Types of Grafts

Adult Tx
- Multivisceral: 24%
- Intest + Liver: 21%
- Intestine: 55%

Pediatric Tx
- Multivisceral: 13%
- Intest + Liver: 50%
- Intestine: 37%
Pre Tx Status by Era

% of Patients

- Home
- Hospitalized

- 1985 - 1990
- 1991 - 2000
- 2001 - 04
- 2005 +
Median Hospital Stay 2005 – 2007

- Intestine
- Intestine + Liver
- Multivisceral

# of Days

0 10 20 30 40 50 60

Slide 86, ITR Complete Data Set, Interim Analysis Sept 5, 2007
Graft and Patient Survival 2002/07

- **Graft Survival (years)**
  - Tx Type: Intestine 384, Intestine + Liver 242, Mod. MV 60, MV 192, Overall 878
  - P = 0.171

- **Patient Survival (years)**
  - Tx Type: Intestine 384, Intestine + Liver 242, Mod. MV 60, MV 192, Overall 878
  - P = 0.112
Rejection @ 3 months

\[ p = 0.024 \]

<table>
<thead>
<tr>
<th>Rej_3M</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>103</td>
</tr>
<tr>
<td>No Rejection</td>
<td>242</td>
</tr>
<tr>
<td>Overall</td>
<td>345</td>
</tr>
</tbody>
</table>
Alive Patient Status > 6 Months Post Tx 2005 - 2007

Graft Function (N=178)

Modified Karnofsky Performance Score (N=163)
Cause of Death Distribution 2005 - 07

- MOF: 60.0%
- Lymphoma: 0.0%
- Rejection: 10.0%
- Technical: 0.0%
- Not Specified: 10.0%
- Thromb/Isch/Bleed: 5.0%
- Cardiac: 5.0%
- Cerebral: 5.0%
- Other: 5.0%

% of Patients
### Univariate Analysis of Factors Affecting Survival

<table>
<thead>
<tr>
<th></th>
<th>Graft</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Tx Status</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Re-Tx</td>
<td>0.0005</td>
<td>0.0010</td>
</tr>
<tr>
<td>Centre Size</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Tx Type</td>
<td>ns</td>
<td>0.0000</td>
</tr>
<tr>
<td><strong>Tx Era</strong></td>
<td>0.0000</td>
<td>0.0352</td>
</tr>
<tr>
<td>Induction Rx</td>
<td>0.0000</td>
<td>0.0007</td>
</tr>
<tr>
<td>Maintenance Rx</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Not significant: recipient gender; recipient age, PRA, donor type, portal vein, and donor blood group compatibility
Intestinal transplant is cost effective within first two years of transplant
Cost and Benefit analysis

• **Cost of TPN per year** $150,000
  Does not include: HPN support, equipment, materials and 0.5-1 admission per year (0-$140,000)

• **Intestinal Transplant is Cost/Effective after the 1-2 years**
Candidates for Intestinal Transplantation

- Multicenter survey in 41 HPN centers from 9 European countries
- 688 adult and 166 pediatric patients
- Potential candidates based on Medicare and Medicaid and USA transplantation society recommendations
- Physician attitudes based on if they would refer potential candidates for transplant

Candidates for Intestinal Transplantation

Conclusions

• A low percentage of candidate patients were considered to be immediate candidates for ITx, suggesting physician reticence toward ITx, a factor which may cause late referral to the waiting list;

• The rate of candidacy differed greatly among the HPN centers, appearing lower in centers taking care of a higher number of HPN patients, whereas data within countries were more homogeneous.
Early referral

- Better Survival Outcome
- Save Organs
- Speed Recovery
- Avoid Narcotic Dependence
- Full Rehabilitation
Trends and future developments

- New immunosuppression drugs
- Rejection Monitoring (Citrulline, Calprotectin)
- Infections prophylaxis and treatment
- Continue studies on ‘tolerogenicity’ of multivisceral graft
Conclusions

• HPN offers the best survival in patients with IF

• Transplant offers the best survival in patients that have developed life threatening complications sec to HPN/IF

• Early referral will prevent HPN related deaths, improve Intestinal Tx outcomes and expand indications
Thank you for all you do for these patients!