Advances in the Management of Intestinal Failure

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Acknowledgements

• Jeffrey Rudolph, Intestinal Care and Rehabilitation Team, Children’s Hospital of Pittsburgh
• Rob Venick, UCLA Medical Center
• David Grant, Intestinal Transplant Association and International Intestinal Transplant Registry
• SRTR and OPTN 2012 Data Report
Objectives

• Review the main causes of intestinal failure in children and adults
• Understand the top trends and changes in intestinal failure management today
• Understand current indications for intestine transplant today
• Understand the outcomes and main management issues following intestinal transplantation

Historical Perspectives

• The field of intestinal rehabilitation began in 1967, Philadelphia, with TPN
• Initiated in surgical loss of intestine
  – Increased post-operative mortality due to inability to nourish patients
• First administered to a newborn infant girl in July, 1967
  – Born with intestinal atresia
  – Duodenocolonic anastamosis
  – Survived 22 months
    • Adequate weight gain
    • Multiple catheters/infections
What is Intestinal Failure?

“A critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements in adults or growth in children.”


Intestinal failure is not a diagnosis: it is a description of a physiological state of organ system dysfunction

Implication of TPN requirement as supportive therapy

Pathophysiology of Short Bowel Syndrome: Considerations of Resected and Residual Anatomy. Tappenden KA. JPEN 2014 May;38(1):16S

Figure 1. (A) Site-specific absorption of dietary nutrients, 2,3 (B) Location of release and primary effects of the major humoral and neural mediators of nutrient processing. SCFA, short-chain fatty acid.
Pathophysiology of Short Bowel Syndrome: Considerations of Resected and Residual Anatomy. Tappenden KA. JPEN 2014 May;38(1):18S

![Image of short bowel syndrome types](image)

Figure 2. Types of intestinal resections: (A) jejunoileal anastomosis, (B) jejunocoelic anastomosis, (C) jejunostomy, and (D) outcomes associated with each type of resection.** PN, parenteral nutrition.

<table>
<thead>
<tr>
<th>Probability of PN dependence</th>
<th>Jejunal Anastomosis</th>
<th>Jejunoileal Anastomosis</th>
<th>Jejunostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low but increased in patients with &lt;35 cm jejunum remaining</td>
<td>Variable* but generally higher in patients with &gt;60-85 cm jejunum remaining</td>
<td>Variable* but higher in patients with &lt;115 cm jejunum remaining</td>
<td></td>
</tr>
<tr>
<td>Possible symptomatic manifestations</td>
<td>Transient gastric and hypoabsorption and impaired digestion</td>
<td>Increased diarrhea; vitamin B₁₂ deficiency; impaired bile salt resorption; deficiency in fat-soluble vitamins; fat malabsorption and steatorrhea; cholestatic cholestasis</td>
<td>Increased stool output; significant ascites and fluid malabsorption; magnesium deficiency; vitamin B₁₂ deficiency; impaired bile salt resorption</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Fair</td>
<td>Fair</td>
</tr>
</tbody>
</table>

* Depending on length of remnant jejunum.

** Chronology of Intestinal Failure

Goals of Intestinal Rehabilitation:

1. Reduce the total time on TPN
   - enteral/oral autonomy
2. Recognize irreversible IF early
   - therapeutic vs. supportive care
3. Minimize complications of intestinal failure

2008: R21 Proposal (funded)
Intestinal failure in children: A contemporary retrospective review by the Pediatric Intestinal Failure Consortium

Criteria for Enrollment

- No more than 12 months old at enrollment
- TPN for 60 out of 74 consecutive days
  - Allow for temporary loss of access or surgery
- Data collection:

```
<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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Study Demographics

typical patient (2000-2004)

Premature: 30-36 weeks EGA
Sick immediately after birth
Fairly short length of bowel
Fair/good synthetic function
At least mild cholestasis

Diagnostic Classification

Table I. Characteristics at birth and at study entry of 272 infants with IF

<table>
<thead>
<tr>
<th>Feature (N = data available)</th>
<th>Number (%)</th>
<th>Median (25th-75th)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156 (57.4)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>204 (61.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>42 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Gestation (wk) (264)</td>
<td></td>
<td>34 (30-36)</td>
</tr>
<tr>
<td>&lt;37 wk (premature)</td>
<td></td>
<td>202 (76.5)</td>
</tr>
<tr>
<td>Birth weight &lt; 2.21 kg (221)</td>
<td></td>
<td>2.1 (1.2-2.7)</td>
</tr>
<tr>
<td>&lt;1.5 kg (very low birth weight)</td>
<td>66 (29.9)</td>
<td></td>
</tr>
</tbody>
</table>

Age when entry criteria met (d) 63 (35, 74)
Small bowel length (cm) 115 (81, 136)

Table II. Diagnoses associated with IF and SBS in infants (N = 272)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>71 (26)</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>44 (16)</td>
</tr>
<tr>
<td>Intestinal atresia (large/ small)</td>
<td>27 (10)</td>
</tr>
<tr>
<td>Volvulus</td>
<td>24 (9 )</td>
</tr>
<tr>
<td>Long segment Hirschprung disease</td>
<td>11 (4 )</td>
</tr>
<tr>
<td>Tufting or microvillus inclusion</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Other single diagnoses</td>
<td>14 (5 )</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Multiple single diagnoses</td>
<td>77 (28)</td>
</tr>
</tbody>
</table>
Outcomes:

In patients (2000-2004):

Overall Mortality: 68/272 (25%)

Those without transplant:

Alive without Tx: 154/272 (57%)
Enteral Autonomy: 118/272 (43%)

**Figure 2.** Outcome for the 272 children on the last date for which data are recorded at the clinical site. Tx, transplant.

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Cause of Death

**Table V.** Cause of death in infants with IF/SBS before and after ITx

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to ITx</td>
<td>58</td>
</tr>
<tr>
<td>Multorgan system failure</td>
<td>28 (62)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Meningitis-palliation</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nephroblastoma-palliation</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13</td>
</tr>
<tr>
<td>Following ITx</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Multorgan system failure</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>
Primary Outcomes

Infectious Complications

As PN progresses, the proportion of Children on PN with infection increases

Figure 1. Percent of patients on PN with septic events by study interval. Time intervals were contiguous, with the designated time coinciding with the mid-point of the interval. The numbers on top of the bars represent the number of children on PN for that study interval.

Figure 3. Primary outcomes: enteral autonomy, death, and intestinal transplantation. The data below the graphs show the cumulative incidence of and the number of children who remain at risk for developing the outcome.
The Genesis of the Intestinal Rehabilitation Team

- After Dudrick’s initial report, the use of TPN spread
  - In pediatrics: clearly in the arena of pediatric surgery
    - Ideal for the management of short bowel syndrome
  - Advancements: introduction of lipids and amino acid solutions
  - Long term survival: reality
  - Use of TPN was used for non-surgical patients with intestinal failure

- The management of intestinal failure developed into a chronic care model
  - Home TPN protocols devised
  - Complexity and diversity of the management issues led to the development of multi-disciplinary teams

Impact of Intestinal Rehabilitation on Medical Systems
Short Bowel Syndrome in Adults: The Need for an Interdisciplinary Approach and Coordinated Care. Matarese LE, Jeppesen PB, O’Keefe SJD. JPEN 2014 May;38(1):63S

Major Complications of TPN Therapy

- Major Morbidities in Intestinal Failure are due to the complications of TPN therapy
- Often the Indications for Small Bowel Transplant
  - Chronic Central Venous Access
    - Vascular Morbidities
    - Catheter Associated Blood Stream Infections
  - Complications due to the Components of TPN
    - Intestinal Failure Associated Liver Disease
    - Role of constituent shortages
      - Copper
      - Thiamine
Treatment Strategies

- Nutritional Strategies
- Pharmacologic Therapies
- Sepsis Prevention
- Hormonal Therapy (GH, GLP-2, EGF)
- Keeping Liver Healthy: Novel Lipid Based Approaches
- Autologous Bowel Reconstruction (STEP)
- Transplantation

Central Venous Catheter Complications

- Central Venous Catheters are a part of everyday life in a child with intestinal failure
- Broken Caths
  - Often from tugging/pulling
  - Trained vascular access team
  - Spiraled lines/holsters/looping
  - Unique Tunneling
- Malocclusions:
  - TPA
- Thrombi
  - Constant manipulation of lines
  - Multiple thrombi: thrombophilia evaluation
Catheter Associated Bloodstream Infections: CLABSIs

- Unique pathogens in the Intestinal Failure Population

Category of Organism

Type of Organism

CCHMC Data: From 6/1/07-6/1/08: N=86 organisms from 75 CA-BSIs

Source of Infection
- External vs. Internal seeding

Recognition
- Soft signs of sepsis
- Potential for decompensation

Line Salvage therapy
- Line locks
  - Antibiotic
  - Ambisome
  - ETOH

Infection Prevention

Management of CLABSIs

External Contamination
Skin Flora
Stool Contamination

Internal Seeding
GI Translocation
Other infections (UTI, cellulitis, osteomyelitis)
CLABSIs: ETOH Lock Prophylaxis

- Presented at IDSA by Judy Martin, MD
- Enrollment IF with >3 CLABSIs
- Prospective, randomized, double blind-crossover
- 25% ETOH lock solution versus placebo (Heparin)
- 12 weeks therapy with 4 week washout followed by 12 weeks of other therapy
- 11 patients completed
- Average lock time 6 hours (4-8)

Current available therapies for SBS patients

**TABLE B. Medications Used in Short Bowel Syndrome (SBS)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-diarrheals</td>
<td>Diphenoxylate Lornipramine</td>
<td>Increase intestinal transit time</td>
</tr>
<tr>
<td>H2 Blockers</td>
<td>Famotidine</td>
<td>Decrease gastric acid secretion</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Omeprazole</td>
<td>Decrease gastric acid secretion</td>
</tr>
<tr>
<td>Pancreatic enzymes</td>
<td>Pancrelipase</td>
<td>Improve digestion</td>
</tr>
<tr>
<td>Somatostatin analogs</td>
<td>Octreotide</td>
<td>Decrease secretory diarrhea</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Metronidazole Trimethoprim</td>
<td>Decrease bacterial overgrowth</td>
</tr>
<tr>
<td>Synthetic conjugated bile acid</td>
<td>Cholic acid</td>
<td>Increase fat absorption</td>
</tr>
<tr>
<td>Trophic factors</td>
<td>Reombinant human growth hormone</td>
<td>Increase nutrient absorption</td>
</tr>
</tbody>
</table>

Matarasse and Steiger. Dietary and medical management of short bowel syndrome in adult patients. 2006 J Clin Gastroenterol

- Medical management
- Bowel lengthening procedures
- Intestinal transplant
GLP-2 secreted mainly from L cells

Sigalet et al. Seminars in Ped Surgery. 2009

Model for the proposed mechanism of action of glucagon-like peptide-2 (GLP-2) on intestinal crypt cells.

Rowland K J, Brubaker P L. Am J Physiol Gastrointest Liver Physiol 2011

©2011 by American Physiological Society
Single hormone therapy: Teduglutide (GLP-2)

- Teduglutide (GLP-2 analog)
- 24 week study of adults with SGS
- 0.05 mg/kg/d vs. placebo (n=43)
  - Significant (20%) reduction in PN use
  - Teduglutide: 27/43 (63%)
  - Placebo: 13/43 (30%)
- All patients on parenteral support >1yr
- No data thus far in children

Intestinal Rehabilitation: Key Questions

- Length of residual bowel and colon
- Underlying disease state
- Status of the liver
Importance of Residual Bowel Length and Colon

Surgical Therapies: Establishment of Continuity
Surgical Adaptation: Bowel Lengthening

Bianchi Procedure

Serial Transverse Enteroplasty (STEP)

Serial Transverse Enteroplasty (STEP)
Survival according to PN indication

Keeping the Liver Healthy

- Prevention of CR-BSIs
  - Sterile technique/line handling
  - ETOH lock therapy
- Advancement of feeds/weaning TPN
- Understanding hepatotoxic effects of TPN
  - Trace elements
  - Glucose
  - Protein
  - Lipids
Intestinal Failure Associated Liver Disease

Early and persistent cholestasis: The UCLA Experience (n=78)

Role of Parenteral Nutrition in IFALD

- Retrospective Review (Boston)
  - 12 patients
  - Dbili >3.0
  - 2/12 improved prior to full enteral nutrition
  - 10/12 complete resolution 4 months after completion

Lipid Emulsions in Parenteral Nutrition Use

- Lipid is an essential nutrient in newborns
  - Requirements (type and amount) not well known
- Soy-based emulsions are only approved form of parenteral lipids in the U.S.

Optimize Lipid Therapy

- Decrease Amount
- Lipid Minimization
- Change Lipid Source

Omegaven®

Algorithm: Hepatic Sparing TPN

- Trial Ursodiol (actigal)
- Reduction of potentially harmful trace elements (Cu, Mn)
- Lipid Minimization (1 g/kg/d)
- Omegaven

Failure to Respond

Poor Weight Gain

Cholestasis-Liver Injury Diagnosed (dbili >2.0)

Exclude other Liver Disease

University of Pittsburgh
IRB# PRO08080394
PI: Jeffrey Rudolph, MD

Personal communication, J Rudolph, Intestinal Care and Rehabilitation Service
Outcomes on Omega-3 Lipid emulsions

Personal communication, J Rudolph Children’s Hospital of Pittsburgh of UPMC

Does the multidisciplinary approach work?

A.S.P.E.N. Clinical Guidelines: Support of Pediatric Patients With Intestinal Failure at Risk of Parenteral Nutrition–Associated Liver Disease
Paul W. Wolfs, Nancy Allen, Patricia Worthington, Donald George, Charlene Conner, the American Society for Parenteral and Enteral Nutrition and Daniel Teitelbaum

3 Retrospective Medical Record Reviews:

<table>
<thead>
<tr>
<th>Survival</th>
<th>Pre-IR Team</th>
<th>Post-IR Team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigalet et al, 2009</td>
<td>73% (33)</td>
<td>100% (22)</td>
</tr>
<tr>
<td>Modi et al, 2008</td>
<td>73% (30)</td>
<td>89% (54)</td>
</tr>
<tr>
<td>Diamond et al, 2007</td>
<td>70% (40)</td>
<td>78% (54)</td>
</tr>
</tbody>
</table>
Decreasing pre-transplant mortality rates among patients wait-listed for an intestinal transplant (SRTR)

Fewer patients waiting for an intestinal transplant
When is the right time for transplant?

TPN VS INTESTINE TRANSPLANT

- Line infection
- Vanishing central Veins
- Liver failure
- Metabolic disorders
- Cost

- Surgery
- Rejection
- Immunosuppression
- ?GVHD

Recipients alive & with a functioning intestinal transplant on June 30 of the year
**Indications for Intestinal Transplantation**

<table>
<thead>
<tr>
<th>U.S.A. Medicare &amp; Medicaid</th>
<th>Am Society of Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPN-Failure</td>
<td>Disease-related risk of death</td>
</tr>
<tr>
<td>• Impending (total bilirubin 3 to 6 mg/dL, progr. thrombocytopenia and splenomegaly) or overt liver failure (portalhypert., hepatosplenomegaly, hepatic fibrosis or cirrhosis)</td>
<td></td>
</tr>
<tr>
<td>• Thrombosis ≥ 2 central veins</td>
<td></td>
</tr>
<tr>
<td>• Frequent and severe CVC sepsis (≥ 2 yr or single episode of fungemia)</td>
<td></td>
</tr>
<tr>
<td>• Frequent episodes of severe dehydration</td>
<td></td>
</tr>
<tr>
<td>Disease-related risk of death</td>
<td></td>
</tr>
<tr>
<td>• Desmoid tumors in FAP</td>
<td></td>
</tr>
<tr>
<td>• Congenital mucosal diseases</td>
<td></td>
</tr>
<tr>
<td>• Ultra short bowel</td>
<td></td>
</tr>
<tr>
<td>High morbidity IF / HPN refusal</td>
<td></td>
</tr>
<tr>
<td>• Poor pain control, frequent hospitalization</td>
<td></td>
</tr>
<tr>
<td>• Pt. unwillingness to continue HPN</td>
<td></td>
</tr>
</tbody>
</table>

*AGA Gastroenterology, 2003  
Kaufman SS, Pediatr Transplant 2001*
When should referral be made for intestine transplantation in children with chronic intestinal failure??

- Infant age
- Evidence of liver disease (jaundice, thrombocytopenia, ascites, splenomegaly, bridging fibrosis
- Primary mucosal disorders
- Massive small bowel resection
- Prognostic or diagnostic uncertainty
- Thrombosis of >/= 2 central veins

Three-year outcomes for patients waiting for an intestinal transplant among new listings in 2009

Intestine Transplant Surgical Techniques:
Choosing the right operation for the right patient at the right time
Disease indications for transplant

Intestinal Transplant Registry Report: Global activity and trends.\textsuperscript{1,2}
D. Grant\textsuperscript{3}, K. Abu-Elmagd\textsuperscript{4}, G. Mazariegos\textsuperscript{5}, R. Vianna\textsuperscript{6}, A. Langnas\textsuperscript{7}, R. Mangus\textsuperscript{8}, D.G. Farmer\textsuperscript{9}, F. Lacaille\textsuperscript{10}, K. Iyer\textsuperscript{11}, T. Fishbein\textsuperscript{12}, and on behalf of the Intestinal Transplant Association AJT Accepted for publication
Changes in transplant type over time

Intestinal Transplant Registry Report: Global activity and trends.1,2
D. Grant3, K. Abu-Elmagd4, G. Mazariegos5, R. Vianna6, A. Langnas7, R. Mangus8, D.G. Farmer9, F. Lacaille10, K. Iyer11, T. Fishbein12, and on behalf of the Intestinal Transplant Association AJT Accepted for publication

Trends in intestinal transplants (SRTR vs ITR)

Intestinal Care and Rehabilitation Center | Children's Hospital of Pittsburgh of UPMC

9/2/2014
Improvements in actuarial survival

**Overall Actuarial Survival**

[Graph showing overall actuarial survival over time with lines indicating 1-year and 5-year survival rates.]


Conditional survival is not changing

[Graph showing conditional survival over time with a flat line indicating no change.]

What are the challenges to long term survival of the intestine recipient?

- Infection and PTLD
- Chronic Rejection
- Immunosuppressant Related Morbidities
  (Renal Failure, Htn, etc)
Immunosuppression use in intestinal transplant recipients

Calcineurin inhibitors (at tx)
Tacrolimus

Anti-metabolites (at transplant)
Mycophenolate
Azathioprine

mTOR inhibitors
At transplant
1 year post-tx

Immunosuppression use in intestinal transplant recipients (continued)

Steroids

Induction agents
IL2-RA
T-cell depleting
None

Year
Percent

Year
Percent

Intestinal Care and Rehabilitation Center
Children's Hospital of Pittsburgh of UPMC
Incidence of first acute rejection among patients receiving an intestinal transplant in 2006–2010

Reported cumulative rehospitalizations among pts receiving an intestinal transplant in 2007–2012
Decision making?

TPN

Intestine Transplant

Current outcomes

Final Considerations

- Current decision making in intestinal failure requires expert multidisciplinary assessment and care
- Understand risk factors, underlying diagnosis, morbidities, and probability of adaptation along with assessment of quality of life
- Improved liver sparing therapy, hormonal therapy and increased non-transplant surgical options are changing the need for intestine transplantation