TOTAL PANCREATECTOMY AND ISLET AUTOTRANSPLANTATION IN CHILDREN

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Disclosure

The speaker has no conflicts of interest or financial ties to disclose.

Chronic Pancreatitis

- DEBILITATING PAIN
  * inability to eat & anorexia
  * malnutrition & weight loss
  * diabetes (endocrine insufficiency)
  * chronic relapsing symptoms

Etiology - Adults

- ethanol use (>100 g/day) 60 - 70%
- idiopathic 20 - 30%
- other causes 10%
  * pancreas divisum
  * hereditary pancreatitis
  * hyperlipidemia
  * autoimmune pancreatitis
  * genetic polymorphisms
    - cystic fibrosis transmembrane conductance regulator (CFTR)
    - pancreatic secretory trypsin inhibitor (SPINK1)

- affects approx. 80,000 people per year
- $65,000,000 annual cost
- 87% adults (mean age 40-50y), 13% children
- 25-fold increased risk of pancreatic cancer
Etiology - Children

<table>
<thead>
<tr>
<th>Chronic pancreatitis patients with history of &gt;1 episode</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute pancreatitis</td>
<td>73</td>
<td>(90)</td>
</tr>
<tr>
<td>Risk factors for pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td>61 (80)</td>
<td></td>
</tr>
<tr>
<td>Prior ERCP</td>
<td>35 (48)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>14 (19)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>11 (15)</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>73 (100)</td>
<td></td>
</tr>
</tbody>
</table>

- 44% male, 56% female
- 7-8 y Abdominal pain
- 5-6 y Dx of CP
- 1-2 y Narcotic use

Schwarzenberg, et al., JPeds 2015

Patient Selection

- Painful chronic pancreatitis or disabling acute relapsing pancreatitis refractory to medical/endoscopic therapy
- Narcotic dependence and/or significantly impaired quality of life
- Imaging/EUS evidence of CP (MRI, MRCP, CT, ERCP) OR relapsing acute pancreatitis (>3 episodes over 6 mos) OR hereditary pancreatitis w/ Sx
- Non-diabetic OR C-peptide positive diabetes
- Patient and family accept (and can manage) risk of diabetes and need for lifelong pancreatic enzyme replacement

Contraindications:

- Active alcohol use (documented abstinence for >6mos)
- Illegal drug use
- Pancreatic cancer (maybe not IPMN)
- Advanced liver, lung, heart disease
- Relative – absent C-peptide

Treatment Options

- Narcotic pain meds, enzyme replacement
- Endoscopic therapies
  - sphincterotomy, stents, dilations
- Celiac plexus ablation
- Surgical decompression (Puestow, Frey, Beger) or partial resection (Whipple, distal)
  - NOT effective in most pts
- Total Pancreatectomy
  - Very effective in most pts, but results in brittle diabetes
- Islet Autotransplant restores endocrine function after TP (TP/IAT)

TP-IAT at UMN

- 1.2% in-hospital mortality; 89% (adult) and 98% (child) 5-y survival
- 90% C-peptide pos., 33% partial function
- 30% insulin independent at 3 y (25% adults, 55% children)
- Pain improved in 85% adults, 94% children (67% pain-free)
- 15.9% had complications requiring reoperation (bleeding, anastomotic leaks)

Sutherland, et al., JACS 2012
Pros and Cons of TP/IAT in Pediatric CP

**PROS:**
- Resolution of chronic refractory pain
- Improved QOL
- Elimination of pancreatic cancer risk

**CONS:**
- High cost
- Prolonged hospital stay
- Irreversible operation
- Life-long dependence on exogenous enzymes
- Diabetes and potential need for chronic insulin therapy
- Absence of counter-regulatory hormones
- GI side effects (dysmotility, malabsorption, diarrhea, malnutrition, etc)

**Timing**
- Earlier is better!
- Prior to development of central sensitization and opioid-induced hyperalgesia which can lead to pain recurrence
- Prior to development of diabetes, malignancy
- Optimization of islet yield/function
  - Prior to invasive surgical procedures (partial resection, ductal drainage)
  - Early in course of disease to minimize fibrosis
Multi-Disciplinary Team Is A MUST!

Gastroenterology  Nursing  Endocrinology
ICU Team  Pain Management  Psychiatry
Islet Manufacture  Surgery  Social Work

The Procedure

Durability of Pain Control

Genetic/Hereditary

![Graph showing Durability of Pain Control](Chinnakotla, et al., JACS 2014)

Nonhereditary

![Graph showing Durability of Pain Control](Chinnakotla, et al., JACS 2014)

Durability of Islet Function

Insulin Requirements

![Graph showing Insulin Requirements](Wilson, et al., Ann Surg 2014)

HbA1c

![Graph showing HbA1c](Wilson, et al., Ann Surg 2014)

**VERY FEW pts developed diabetes-related complications**

Chinnakotla, et al., JACS 2014

TP-IAT Particularly Effective in Children with CP

Narcotic Use

Insulin Independence

School Attendance and Days of Impaired Activity

Islet Function and Insulin Independence

- 25-40% insulin independent in most large cohorts
- Most insulin dependent patients have graft function
  - Low insulin needs
  - + C-peptide (nearly 90%)
- Benefit of islets, even if on insulin
  - Stable glycemic control
  - Avoid “brittle” (labile) diabetes
  - Absent hypoglycemic episodes

QOL by SF-36 Assessment - Children

Sutherland et al., Transplantation 2008
Ahmed et al., JACS 2005
Webb et al., Pancreas 2005


Bellin, et al., UMN data
Who Becomes Insulin Independent?

**Predictors:**

- **Islet number (mass/yield)**
  - 100% function, 70% independent with >5000 IE/kg
  - 83% function, 30% independent with 2501-5000 IE/kg
  - 59% function, 15% independent with <2500 IE/kg
- **Prior surgery**
  - Lower yield after surgical drainage/distal pancreatectomy
- **Age**
  - Younger patients have higher rates of insulin independence
- **Other characteristics**
  - Duration of disease, islet quality, insulin resistance

Insulin Independence and IEQ/Kg

- 6 months
- 12 months
- 24 months
- 36 months

Islet Yield and Prior Pancreatic Surgery

<table>
<thead>
<tr>
<th>IEQ/Kg</th>
<th>Baseline</th>
<th>Whipple</th>
<th>Beger/Frey</th>
<th>Distal</th>
<th>Puestow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>3795</td>
<td>3647</td>
<td>2654</td>
<td>1973</td>
<td>1883</td>
</tr>
</tbody>
</table>

High Likelihood of Insulin Independence in Young Children

- Children 5-18 years of age:
  - 44% ever achieve insulin independence
  - 85% of children <10 years of age have documented insulin independence

Sutherland et al., Transplantation 2008
Ahmad et al., JACS 2005
Webb et al., Pancreas 2008
Islet Neogenesis in Children with CP

Interconnected duct-like (arrows) and endocrine structures (arrowheads) surrounded by fibrosis

Insulin pos. cells surrounded by duct-like structures

Islets separate from ductal issue

UCSF Inpatient Care Algorithm

Day 1
PCA
Start TF/enzymes
IV Anti-emetics
NG out/GT to gravity, NPO
Insulin drip
Ambulate to chair
Consult Endocrine, Pain Svcs

Day 2
PCA
TF/enzymes
IV Anti-emetics
Insulin drip
Ambulate x1
Order PT/OT Eval & Treat

Day 3
PCA transition basal to long-acting TF/enzymes
IV Anti-emetics
Insulin drip
Ambulate x3

Day 4-5
PCA transition to short acting elixir
Oral pain meds
TF at goal
Bowel Regimen
Start Lantus, D/C insulin drip
Start Diabetic education

Day 6
ADAT
Start TF education/Discharge class
Bowel Regimen
Continue plan, eval for complications

Day 7-8
Supplement education prn
Continue plan, eval for complications

Consider transfer to Home/Rehab when following are met:
TF stable
Adequate water intake to prevent IV depletion/dehydration
Diabetes stable, not requiring daily titration of Diabetes therapy
No surgical concerns
Narcotic dose stable, < 3 extra IV doses/day

UCSF Experience

- 2004 - 2015: 28 cases
- 22 cases since 2014 (50% male, 8 children)
- Mean age 38 years (range 4 to 72)
- 10 islet isolations for other centers

- Etiologies of CP:
  - idiopathic/familial 60%
  - pancreas divisum 10%
  - remote alcohol abuse 30%
  - biliary disease 0%

- Prior pancreatic surgery
  - Puestow procedure 33%
  - distal pancreatectomy 25%
  - pancreaticoduodenectomy 8%

Pediatric TP/IAT at UCSF

8 Children (2013-2016)

<table>
<thead>
<tr>
<th>Pt</th>
<th>DOS</th>
<th>Dx</th>
<th>Age</th>
<th>Weight</th>
<th>IEQ</th>
<th>IEQ/kg</th>
<th>Current Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/7/13</td>
<td>CFTR/SPINK</td>
<td>10</td>
<td>32 kg</td>
<td>264,234</td>
<td>8,257</td>
<td>full (has T1DM)</td>
</tr>
<tr>
<td>2</td>
<td>2/10/14</td>
<td>PRSS1</td>
<td>12</td>
<td>41 kg</td>
<td>185,840</td>
<td>4,425</td>
<td>5-10U/d</td>
</tr>
<tr>
<td>3</td>
<td>5/7/15</td>
<td>P. Divisum</td>
<td>16</td>
<td>50 kg</td>
<td>432,200</td>
<td>7,582</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>9/8/15</td>
<td>SPINK</td>
<td>4</td>
<td>17 kg</td>
<td>186,600</td>
<td>10,724</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4/4/16</td>
<td>PRSS1</td>
<td>7</td>
<td>24 kg</td>
<td>207,680</td>
<td>8,652</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>5/24/16</td>
<td>PRSS1</td>
<td>10</td>
<td>41 kg</td>
<td>331,420</td>
<td>8,163</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>5/26/16</td>
<td>CF/SPINK</td>
<td>14</td>
<td>69 kg</td>
<td>688,822</td>
<td>9,983</td>
<td>weaning (5mos)</td>
</tr>
<tr>
<td>8</td>
<td>8/1/16</td>
<td>CF</td>
<td>16</td>
<td>124 kg</td>
<td>187,400</td>
<td>1,551</td>
<td>weaning (2mos)</td>
</tr>
</tbody>
</table>

MEAN±SD 11.4±4.3 310.547±7.412 0.3028

- 4/8 pain-free off narcotics
- 2/8 weaning (intermittent narcotics only)
- 2/8 managed in LA (at least 1 weaning)
**Patient 4**

**Clinical History**
- 3yo female presented with pancreatitis (SPINK1 mutation) in December 2014
- Conservative management with NPO, TPN, narcotics
- Developed pseudocyst, multiple ERCPs
- Transferred to UCSF
- Found to have pancreatic leak with pseudocyst, fistulous communication to chest causing mediastinitis, pulmonary embolism, left lung

**Surgical Course:**
- 06/24/15 – surgical cystgastrostomy – no improvement
- 07/11/15 – VATS, washout of thoracic cavity and mediastinum, left with 2 chest tubes and 1 mediastinal tube
- 07/19/15 – ex-lap, peritoneal drain placement – some improvement
- TP/IAT 9/8/2015, pancreas inflamed, extremely fibrotic 186,600 IEQ (10,724 IEQ/kg) infused intraportally

**Pediatric Patient 4**

**Lengthy post-op hospitalization** – pain control, nutrition
- Now 1 year out, off pain meds, tolerating regular diet and going to Kindergarten

**Summary – TP/IAT**
- TP/IAT is very effective in relieving pain while minimizing risk of labile diabetes
- Diabetes outcomes are best with high yield, surgically naïve pancreas, young children
- Long-term insulin independence and robust insulin secretory capacity are feasible
- Overall benefit of the procedure is markedly compromised w/o IAT, but many insurance carriers do not cover
Thank You!

Islet Isolation:
- Florinna Dekovic
- Vinh Nguyen
- Greg Szot

Clinical Team:
- Michelle Klosterman
- Marilyn McEnhill
- James Ostroff
- Emily Perito
- Sue Rhee
- Steve Gitelman
- Roger Long
- Ramana Naidu
- Kara Campbell
- Neesha Mehta
- The transplant surgeons