TOTAL PANCREATECTOMY AND ISLET AUTOTRANSPLANTATION AS TREATMENT FOR CHRONIC PANCREATITIS
Andrew Posselt, MD, PhD
Dept. of Surgery
University of California, San Francisco

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Chronic Pancreatitis
benign disease of the pancreas characterized by:
- 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>Etiology</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Chronic pancreatitis with history of m/c episode</td>
<td>70%</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>30%</td>
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<tr>
<td>Radiation-related pancreatitis</td>
<td>7%</td>
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<tr>
<td>Alcohol-related pancreatitis</td>
<td>3%</td>
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<tr>
<td>Endocrine disease</td>
<td>10-20%</td>
</tr>
<tr>
<td>Infection of islet cells</td>
<td>1-3%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1-2%</td>
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- Mean age: 14 y (35% 5-12 y, 65% 13-19 y)
- 44% male, 56% female
- 7-8 y Abdominal pain
- 5-6 y Dx of CP
- 1-2 y Narcotic use

**Time to Onset of Diabetes Mellitus**

- 50% at 10 years after symptom onset, 80% at 25 years
- Many continue to be c-peptide positive

**Treatment Options**

- Narcotic pain meds, enzyme replacement
- Endoscopic therapies
  - sphincterotomy, stents, dilations
- Celiac plexus ablation
  - chemical, surgical
- 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)

**Indications for TP-IAT**

- 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
Timing

- Earlier is better!
- Prior to development of central sensitization and opioid-induced hyperalgesia which can lead to pain recurrence
- Optimization of islet yield/function
  - Prior to invasive surgical procedures (partial resection, ductal drainage)
  - Prior to glucose intolerance/diabetes
  - Early in course of disease to minimize fibrosis
  - Younger children (fewer post-op complications and higher islet yields)

Pediatric TP/IAT Cases by State: 1977-2016

Multi-Disciplinary Team Is A MUST!

- Gastroenterology
- Nursing
- Endocrinology
- Pain Management
- Psychiatry
- Social Work
- Surgery
**The Procedure**

Patient's OWN islets
No risk of rejection
No immunosuppression

**UCSF Inpatient Care Algorithm**

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

**Day 2**
- PCA
- Start TF/enzymes
- IV Anti-emetics
- Insulin drip
- Ambulate 1
- 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
- Bowel/Regimens
- Start Lantus, D/C insulin drip
- Start Diabetic education

**Day 6**
- Start TF education/Discharge class
- Bowel/Regimens
- Continue plan, eval for complications

**Day 7-8**
- Discharge 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

**TP-IAT at UMN**

- 1.2% in-hospital mortality; 89% (adult) and 99% (child) 5y survival
- 90% C-peptide pos., 33% partial function
- 30% insulin independent at 3 y (25% adults, 55% children)
- Pain improved in 83% adults, 94% children (87% pain-free)
- 15.9% had complications requiring reoperation (bleeding, anastomotic leaks)

**Pain Relief**

- In patients with CP whose pain persists after Endoscopic Duct Drainage (EDD) procedures, TP-IAT can:
  - Provide pain relief in the majority of patients
  - Give the chance to wean off narcotics
  - Preserve insulin secretion in most
  - Improve quality of life

- Effort is needed to identify in advance the few patients whose life will not be made better by TP-IAT
Durability of Pain Control

Genetic/Hereditary

Nonhereditary

Pain severity

QOL by SF-36 Assessment

QOL: Improved in 80%; Same in 15%; Worse in 5%

- 98% preferred diabetes to former pain
- 87% said pancreatitis was worse than diabetes
- 98% would have procedure again

School Attendance and Days of Impaired Activity

Proportion with school absence due to health

Number of days activity was limited per 4 weeks

P<0.001

P<0.005

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

Sutherland et al., Transplantation 2008
Ahmad et al., JACS 2005
Webb et al., Pancreas 2008
Sutherland et al., Transplantation 2008
Ahmad et al., JACS 2005
Webb et al., Pancreas 2008
Durability of Islet Function

Very few pts developed diabetes-related complications

TP-IAT Particularly Effective in Children with CP

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
  - Pediatric patients have high rates of insulin independence
- Other characteristics
  - Duration of disease, islet quality, insulin resistance

Insulin Independence and IEQ/Kg
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

Islet Autotransplants Function Better Than Allotransplants

- Fewer islets needed (2500IE/kg vs. >7500IE/kg)
- Most function >2yrs, approx 80% >3-4yrs; 70% >10yrs
- No ‘late’ failures

UCSF Experience

- 32 adults since 2013 (8-10/y since 2016)
- 14 children (10 since 2015)
- 12 isolations for pts at UCLA
- Referrals from CA, NV, AL, AZ, CO, NY, TX, WA, Kaiser

- Mean hospital stay: 16d (10-60d)
- Readmissions: 2 within 30d, 3 within 6 mos
- Complications: bleeding (2), SBO (2), N/V (1)
- Mean IEQ/kg: 5700±2000 (a), 7,400±176,000 (p)
- Insulin independence: 60% adults, 87% peds
- Pain control: 60% adults off meds, 40% weaning 100% peds off meds

Insurance Coverage is a Problem!

- All carriers cover TP, but only some cover AIT
- AIT adds approx. $27,000-30,000 to overall cost.
- OR time not significantly prolonged since isolation is performed during biliary and intestinal reconstruction, and infusion takes approx. 20 mins.
- Overall LOS, hospitalization costs not significantly increased
- QOL dramatically increased with AIT even if independence is not achieved, but most pts cant raise adequate funds to cover procedure.
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

Thank You!

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