

“Islet” Them Take My Whole Pancreas!

Jaimie D. Nathan, MD
Surgical Director, Pancreas Care Center
Cincinnati Children's Hospital Medical Center

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Disclosures

- In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.



Objectives

- Review surgical drainage procedures and resections for chronic pancreatitis
- Recognize indications and patient evaluation process for total pancreatectomy and islet autotransplantation (TPIAT)
- Understand outcomes following total pancreatectomy and islet autotransplantation



Chronic Pancreatitis (CP)

- Progressive, irreversible damage to pancreas
 - Numerous etiologies in children
- Varying inflammation, scarring, pancreatic duct abnormalities, exocrine atrophy, secondary involvement of islets
- Variable degree of pain, exocrine insufficiency, occurrence of diabetes

Hallmark: intractable and debilitating pain, with poor quality of life



Overall Treatment Goals

- To relieve acute and chronic pain
- To calm disease process to prevent repeated attacks
- To correct metabolic consequences
 - Malnutrition
 - Diabetes
- To manage complications of chronic pancreatitis

When maximal medical therapies and endoscopic approaches fail to relieve pain and to address specific complications, surgical procedures may be considered

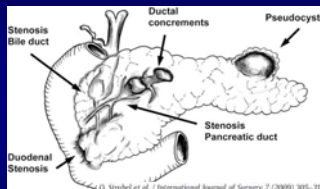


Indications for Surgery

- Approximately 50% of CP patients eventually require surgery¹

- **Classic indications:**

- Bile duct obstruction
- Duodenal obstruction
- Pseudocysts
- Suspicion of malignancy
- Debilitating pain that fails to respond to medical and endoscopic treatment options – **most common**



© G. Strobel et al. / International Journal of Surgery 7 (2009) 305–312

¹Mitchell et al. Lancet 2003;361:1447-1455.



Overall Aims of Surgery

- To provide long-term relief of pain and improve QOL
- To ensure low risk of morbidity or mortality
- To preserve as much pancreatic tissue as possible to preserve function
 - Exocrine function
 - Endocrine function
- To resolve complications involving adjacent organs



Timing of Surgery

- Few studies have examined optimal timing
 - Earlier surgery may be more beneficial by delaying progressive destruction of parenchyma¹
 - Some studies have reported that surgery within 3 years of symptom onset may achieve better pain relief²
 - Because surgery is not uniformly successful in all patients, others advocate "watch and wait" approach

No clear consensus on timing of surgery for CP

¹Nealon et al. Ann Surg 1993;217:458-466.
²Ahmed Ali et al. Cochrane Database Syst Rev 2012.



Approach to Surgery

No single surgical procedure recommended for all patients with chronic pancreatitis

- Procedure selected on basis of:
 - Severity of pain
 - Pancreatic duct abnormalities
 - Extent of pancreatic tissue disease
 - Presence of local complications
 - Overall condition of patient



Approach to Surgery

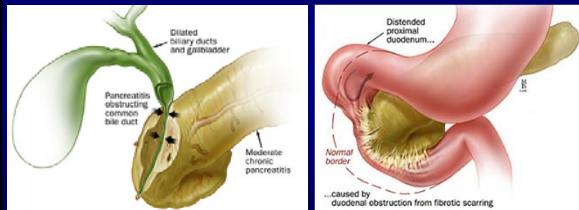
No single surgical procedure recommended for all patients with chronic pancreatitis

- Types of surgical procedures:
 - Bypass procedures
 - Drainage procedures
 - Partial pancreatic resections
 - Combination of drainage + partial resection
 - Total pancreatectomy with islet autotransplantation



Treatment of Obstruction

- Due to inflammation and scarring in pancreatic head, bile duct or duodenum may become obstructed



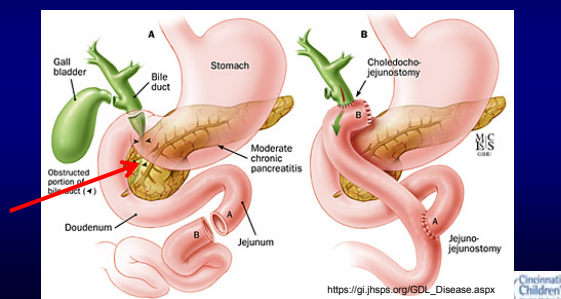
https://gi.jhsp.org/GDL_Disease.aspx

For mechanical obstruction in absence of pancreatic pain, most will consider bypass procedures



Biliary Obstruction

- **Choledochojejunostomy:** Roux-en-Y jejunal limb sutured to bile duct to allow bile to drain from liver into intestine

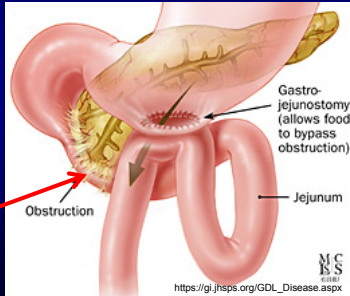


https://gi.jhsp.org/GDL_Disease.aspx



Duodenal Obstruction

- **Gastrojejunostomy:** Proximal jejunum sutured to stomach to allow for gastric contents to bypass obstructed duodenum



https://gi.jhsps.org/GDI_Disease.aspx



Pancreatic Pseudocysts

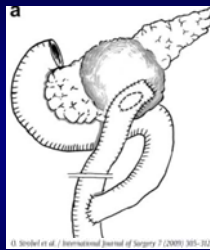
- Collection of pancreatic fluid outside normal confines of duct system
- Common complication in CP (25%)
- Most resolve spontaneously
- **Surgery considered if symptoms are persistent, cyst is enlarging, or complications occur, and endoscopic & interventional approaches fail**



https://gi.jhsps.org/GDI_Disease.aspx

Cystgastrostomy

opening in pseudocyst wall is sutured to posterior wall of stomach

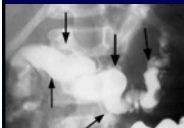


Cystjejunostomy

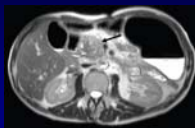
opening in pseudocyst is sutured to Roux-en-Y jejunal limb



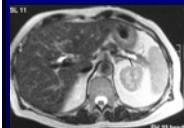
Treatment of Pain



Large duct disease



Inflammatory mass in head of pancreas



Distal stricture with focal disease



Minimal change disease

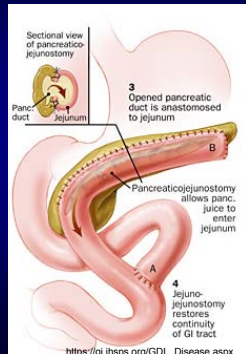
Preoperative assessment of morphology of disease determines the most appropriate surgical procedure



Large Duct Disease

• Longitudinal Roux-en-Y pancreaticojejunostomy

- Partington-Rochelle "modified Puestow" procedure
 - Drainage procedure
- Dilated pancreatic duct is opened lengthwise and Roux jejunal limb is sewn to longitudinally opened duct
- Simple, low risk of complications
- Preserves pancreatic tissue

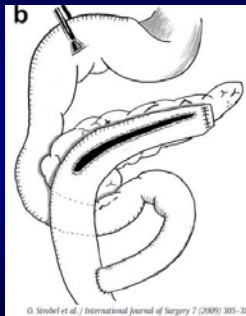


https://gi.ihps.org/GDI_Disease.aspx

Large Duct Disease

• Longitudinal Roux-en-Y pancreaticojejunostomy

- Short-term pain relief in 75%
- Recurrent pain in >50%¹
 - Incomplete duct decompression or continued inflammation in head
- Current indication:
 - Isolated PD dilation (>7mm) or "chain of lakes" **without** inflammatory mass in head & **without** hereditary etiology



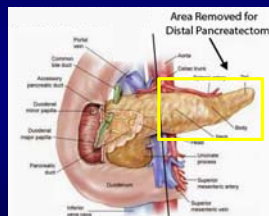
© Strobel et al. / International Journal of Surgery 7 (2009) 305-312

¹Laje et al. J Ped Surg 2013;48:2271-2275.

Distal Stricture/Focal Disease

• Distal pancreatectomy

- May be considered if predominant disease is in body/tail of pancreas
 - Isolated duct stricture or pseudocyst disease
- Resection of pancreas to left of portal vein
- Low risk of complications, mortality, especially if spleen preserved

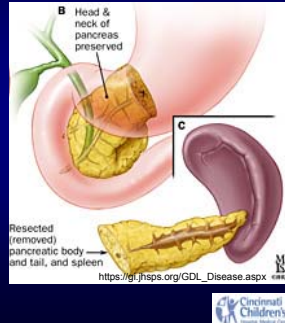


Cincinnati Children's

Distal Stricture/Focal Disease

• Distal pancreatectomy

- Drawback:
 - Pain often recurs within a few years, because disease in head has not been addressed
- Limited current utility in CP:
 - Local tail complications
 - Pseudocysts
 - Pseudoaneurysms



Enlarged Head

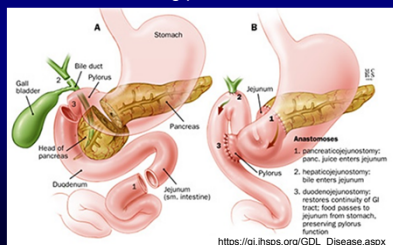
- Many CP patients present with inflammatory enlargement of head of pancreas which causes obstruction of main pancreatic duct
 - "Pacemaker" of disease
- Several surgical approaches for this disease variant have been assessed
 - Some randomized controlled trials in adults
 - Few reports and series in children
- Types of surgical procedures:
 - Partial resection (pancreaticoduodenectomy)
 - Combination of drainage + partial resection



Enlarged Head

• Pancreaticoduodenectomy ("Whipple")

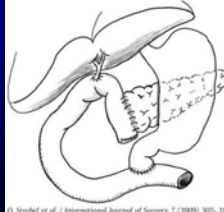
- Utilized for treatment of pain and the complications of CP
- Rationale: eliminates obstructive mass in head of pancreas and drains the remaining pancreatic duct



Enlarged Head

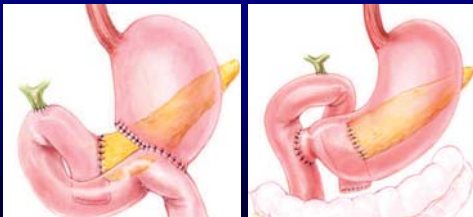
- **Pancreaticoduodenectomy ("Whipple")**

- Major advantage: complete resection of head removes possibility of disease recurrence originating in head
- Major disadvantage: surrounding non-diseased organs (bile duct, duodenum) are sacrificed and require reconstruction
- Low mortality (<0 – 5%)
- High morbidity (>40%)
 - Major cause: anastomotic leak
- Pain relief in 71 – 89% at 4 – 6 yrs



Pancreaticoduodenectomy ("Whipple" procedure)

- "Standard" Whipple or pylorus-preserving technique
- Three anastomoses: pancreatic, biliary, gastrointestinal
- Late endocrine and exocrine dysfunction in up to 50%
- **Uncommonly utilized in children with CP**



Cameron et al. Atlas of Gastrointestinal Surgery 2014.



Enlarged Head

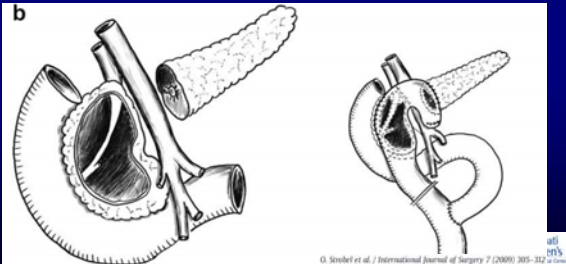
- **Duodenum-preserving pancreatic head resection (DPPHR)**

- Combined drainage + partial resection
- Rationale: achieve benefits of extensive head resection and decompression of pancreatic duct, while preserving bile duct and gastrointestinal continuity
- Three primary operations have evolved:
 - Beger procedure
 - Berne procedure
 - Frey procedure



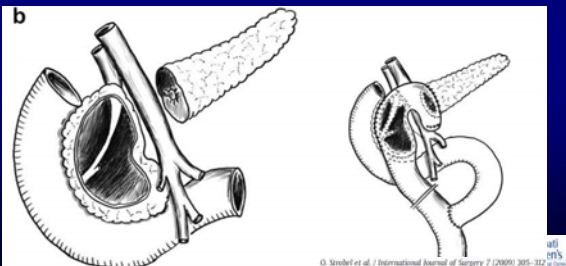
Beger Procedure

- Resection of pancreatic head, leaving rim along duodenum, with division of pancreas over portal vein
- Reconstruction: Roux jejunal limb sutured to distal pancreas and to remnant rim along duodenum (two anastomoses)



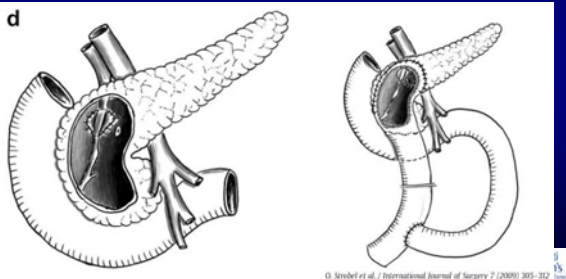
Beger Procedure

- Pain relief in 80 – 85% of patients, well-maintained at 5 yrs
- Low mortality (0 – 3%); morbidity = 15 – 32%
- Preserves fxn with minimal exocrine/endocrine insufficiency



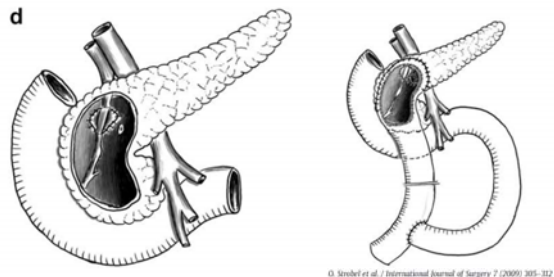
Berne Procedure

- Technical simplification of Beger procedure: extent of head resection is same, but no dissection over portal vein
- Reconstruction: single anastomosis of Roux jejunal limb to pancreas resection cavity



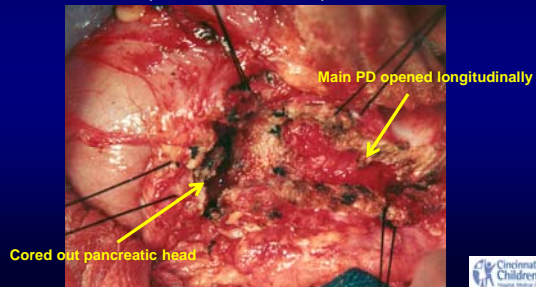
Berne Procedure

- Pain relief in 85 – 89% of patients
- Low mortality (0 – 1%); morbidity = 20 – 23%
- Equivalent pain and QOL outcomes vs. Beger procedure



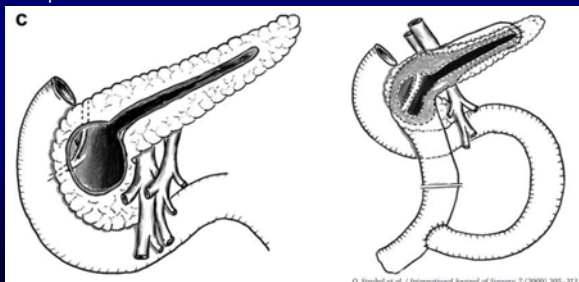
Frey Procedure

- More limited head excavation than Beger procedure
- Main pancreatic duct opened along its course to tail
- Pancreatic neck preserved → lower operative risk



Frey Procedure

- Reconstruction: Roux limb of jejunum sutured to resection cavity and along length of pancreatic duct
- Indication: smaller inflammatory mass in head with distal pancreatic duct obstruction and dilation



Frey Procedure

- Pain relief in >85% of patients
- Low mortality (<1%); morbidity = 9 – 39%
- Well-maintained exocrine and endocrine function

Frey Procedure for Surgical Management of Chronic Pancreatitis in Children
Journal of Pediatric Surgery, Vol. 39, No. 6 (June), 2004, pp 817-820
 By Michael D. Rollins and Rebecca L. Meyers
 Salt Lake City, Utah

- 8 of 11 children had excellent or good results after Frey

Frey procedure for chronic pancreatitis in children: A single center experience¹²

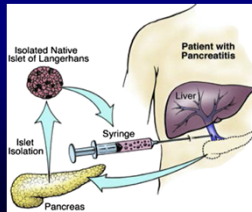
Sukanta Ray*, Sumit Sanyal, Supriyo Ghatak, Sujat Khamrui, Jayanta Biswas, Suman Saha, Tuhin Subhra Mandal, Gautam Chattopadhyay
Journal of Pediatric Surgery (2015) 50A-508

- 91% of children (n = 24) remained pain-free with median follow-up of 29 months



Although conventional surgeries for CP result in initial pain relief, pain recurs in more than 50% of patients over the long-term

Failure of conventional surgery is considered an indication for total pancreatectomy with islet autotransplantation (TPIAT)

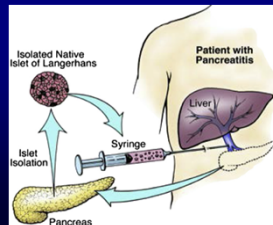


Minimal Change Disease

- Diffuse inflammatory process and scarring
 - Absence of gross morphologic changes
 - Histologic evidence of chronic inflammatory destruction of parenchyma
 - No main duct dilation or inflammatory mass
 - Drainage procedures and resections not useful
- Pain is debilitating and refractory to medical and endoscopic approaches
 - TPIAT is utilized to treat refractory pain



Total pancreatectomy with islet autotransplantation (TPIAT)



TPIAT

- First performed in 1977 at University of Minnesota
 - First TPIAT in a child in 1989
- **Primary goals:**
 - To relieve incapacitating pain
 - To eliminate need for narcotics
- **Goal of IAT:**
 - To preserve β -cell mass & insulin secretory capacity
 - To prevent or minimize otherwise inevitable brittle diabetes
- IAT is **not** considered experimental and is covered by most 3rd party payers in U.S.



TPIAT Patient Selection

- Highly-selected patient subgroup with intractable pain or frequent occurrences of acute attacks to the point of incapacitation, with one of the following:
 - No conventional operative option
 - Failure of prior conventional surgery
 - Idiopathic or genetically-linked recurrent acute pancreatitis
- Lower threshold may be considered for patients with hereditary pancreatitis associated with an elevated risk of progression to pancreatic cancer (eg. PRSS1)



Contraindications

- **To IAT:**
 - Pre-existing IDDM
 - Advanced NAFLD, other parenchymal liver disease
 - Portal hypertension, portal vein thrombosis
- **Poor candidates for TPIAT:**
 - Visceral hyperalgesia
 - “Functional” pain
 - Severe psychosocial maladaptation, drug-seeking behavior



CCHMC Patient Evaluation

- **Multidisciplinary**
 - Pediatric transplant surgeon
 - Gastroenterologist
 - Endocrinologist
 - Pain team
 - Psychologist
 - Geneticist
 - Dietician
 - Social worker
- **Studies**
 - Cross-sectional imaging (MRI/MRCP)
 - ERCP
 - Genetic testing
 - Exocrine function testing (stool, direct)
 - Mixed-meal tolerance testing



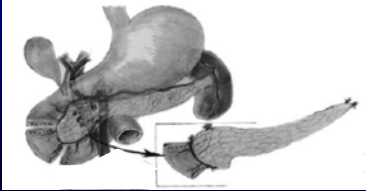
CCHMC Criteria for TPIAT

- Diagnosis of chronic pancreatitis or acute recurrent pancreatitis by objective criteria
 - Cross-sectional imaging, EPI, histopathology, genetics
- Chronic pain >6 mos duration with daily narcotic use or severely impaired QOL, with adequate interventions by Pain team
- Absence of reversible cause of pancreatitis
- Failure of medical and endoscopic interventions
- Adequate β -cell function
- No physiologic or psychosocial contraindication



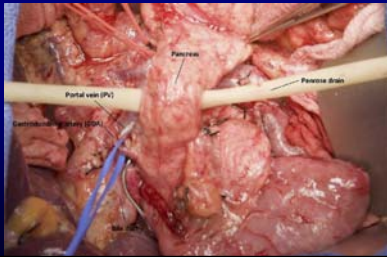
TPIAT Procedure

- Total pancreatectomy
- Partial duodenectomy (D1 preserved)
- Splenectomy
- Cholecystectomy

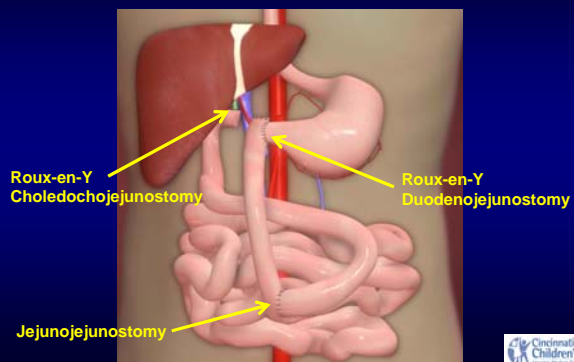


Surgical Considerations

- Blood supply to pancreas preserved until just before resection to avoid warm ischemia
- GI reconstruction after removal of pancreas

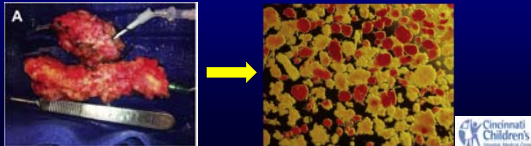


GI Reconstruction



Islet Preparation and Infusion

- Anticoagulation with heparin (70 U/kg)
- Infused slowly via splenic vein stump with measurement of portal pressures
- If pressure >25 cm H₂O, infusion is stopped to allow autoregulation
- Strict blood glucose control – insulin infusion



Postoperative Management

- Doppler Ultrasound
- Strict blood glucose control (80 - 120) to prevent hyperglycemic injury to islets
 - Continuous glucose monitor
- Individualized pain management plan
- Heparin infusion x 7 days
- Dextran infusion x 48 hrs to prevent instant blood-mediated inflammatory response, followed by aspirin
- Tube feeds via J-port of GJ tube
- Pancreatic enzyme replacements



Surgical Complications

- Overall rate ≈ 15 – 20%
- Bleeding (5 – 7%)
- Intra-abdominal abscess, wound infection (5%)
- Small bowel obstruction (5%)
- Portal vein thrombosis (2 – 4%)
- Enteric leak from GI anastomoses (3%)
- Bile leak (1 – 2%)
- Systemic inflammatory response syndrome
- Delayed gastric emptying
- GI bleeding (gastritis, ulcer)



Outcomes of TPIAT in Children

- Improvement in pain and QOL scores¹
- Higher rates of insulin independence, versus adults²
 - In children <12 yo, 55% insulin independent and 30% with partial islet function
 - Greater # islets for body weight and lower insulin demands
 - Higher replicatory capacity³; islet neogenesis of ductal origin⁴
- Islet function durability especially good for pts <21 yo and those with short history of pancreatic disease⁵
 - Most with excellent islet function at 3 yrs remain off insulin for years despite growth into adulthood

¹Bellin et al. Clin Gastroenterol Hepatol 2011;9:793-799.

²Sutherland et al. J Am Coll Surg 2012;214:409-424.

³Meier et al. Diabetes 2008;57:1584-1594.

⁴Soltani et al. Acta Diabetol 2013;50:807-814.

⁵Bellin et al. Curr Diab Rep 2010;10:326-331.



TPIAT in Children

Total Pancreatectomy and Islet Autotransplantation in Children for Chronic Pancreatitis

Indication, Surgical Techniques, Postoperative Management, and Long-Term Outcomes

Srinath Chinnakotla, MD,* | Melissa D. Bellin, MD,† | Sarah J. Schwarzenberg, MD,‡ |
David M. Radsuevich, PhD, RN,* | Marie Cook, MPH,* | Ty B. Dunn, MD,* | Gregory J. Bellman, MD,*
Martin L. Freeman, MD,§ | A. N. Balasubramanian, PhD,* | Josh Wilhelm, MS,‡ | Barbara Bland, MS, RN,*
Jose M. Jimenez-Vega, MD,‡ | Bernhard J. Hering, MD,* | Schwyn M. Vickers, MD,* | Timothy L. Pruett, MD,*
and David E. R. Sutherland, MD, PhD*†

Annals of Surgery • Volume 260, Number 1, July 2014

Largest series of children with CP treated with TPIAT

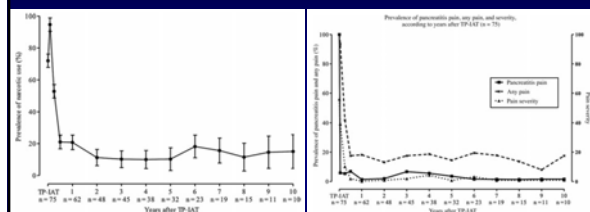
University of Minnesota

75 patients

1989 – 2012



Pain Outcomes



Significant reduction in narcotic use after TPIAT.

Reduced prevalence of pancreatitis pain and severity of pain.

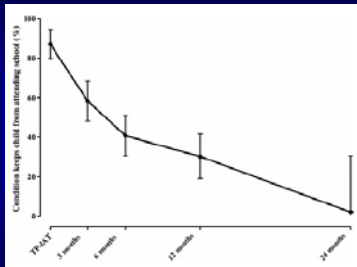
Nearly all improvement in pancreatitis pain occurred in first 3 months.

Effects are sustained over time.

Chinnakotla et al. Ann Surg 2014;260:56-64.



Lost School Days

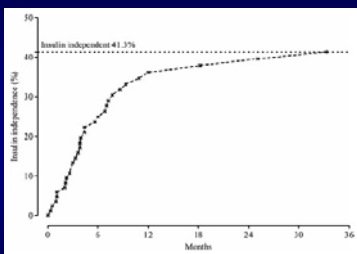


Percentage of parents reporting lost days at school statistically declined from 87% to a negligible value at 2 years post-TPIAT.

Chinnakotia et al. Ann Surg 2014;260:56-64.



Insulin Independence Over Time

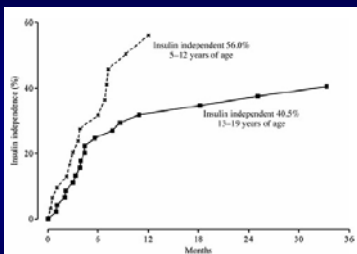


Insulin independence achieved in 41.3%.
28 of 31 pts achieved insulin independence within 12 mos after TPIAT.

Chinnakotia et al. Ann Surg 2014;260:56-64.



Insulin Independence by Age

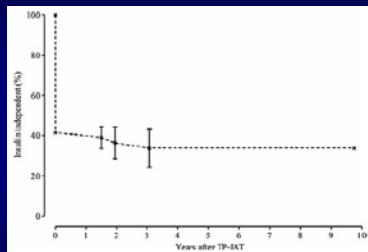


Younger children (<12 yo) were more likely (56%) to achieve insulin independence than older children (40.5%).

Chinnakotia et al. Ann Surg 2014;260:56-64.



Insulin-free Survival



Insulin independence observed for as long as 10 years after TPIAT.
3 of 31 patients reverted to partial graft function.

Chinnakotla et al. Ann Surg 2014;260:56-64.



Insulin Independence by IE/kg

TABLE 4. Islet Function Status According to Number of Islet Equivalents per Kilogram Transplanted

	6 mo		12 mo		24 mo		36 mo		C-Peptide-Positive (>0.6 ng/mL), %	HbA _{1c} With Mean <7.0%
	n	%	n	%	n	%	n	%		
<2500 IE/kg	15		15		15		10		84	81
Insulin independent	2	13	2	13	2	13	1	10		
Partial function	8	53	6	40	6	40	3	30		
Insulin dependent	5	33	7	47	7	47	6	60		
2500-5000 IE/kg	17		17		17		14		100	96
Insulin independent	5	29	9	53	9	53	7	50		
Partial function	12	71	8	47	5	29	4	29		
Insulin dependent	0	0	0	0	3	18	3	21		
>5000 IE/kg	17		17		17		12		100	100
Insulin independent	9	53	13	76	13	76	11	92		
Partial function	7	41	3	18	3	18	1	8		
Insulin dependent	1	6	1	6	1	6	0	0		

Insulin independence is dependent on number of islet equivalents (IE) transplanted per kg body weight.

Chinnakotla et al. Ann Surg 2014;260:56-64.



Conclusions

- Surgery plays a key role in treatment of children with CP and is considered when maximal medical therapies and endoscopic approaches fail to relieve pain and to address complications
- Comprehensive multidisciplinary patient evaluation is critical to ensure optimal surgical management
- Conventional operations can provide long-term pain relief and improvement in QOL in children with CP
- In appropriately selected children, TPIAT achieves durable pain relief and improves QOL with manageable glycemic control



Questions?

CCHMC Pancreas Care Center Team

- Gastroenterology
- Surgery
- Radiology
- Pain Team
- Endocrinology
- Genetics
- Oncology
- Nurses
- Social Work
- Psychology
- Child Life
- CRC, Statistician