Betul Hatipoglu, MD
Clinical Associate Professor of Medicine,
Staff
Endocrinology & Metabolism Institute Cleveland Clinic
Figure 1. Annual number of US pancreas transplantations reported to UNOS/IPTR, 1966-2010.
ADA RECOMMENDATIONS

• Pancreas transplantation should be considered an acceptable therapeutic alternative to continued insulin therapy in diabetic patients with imminent or established end-stage renal disease who have had or plan to have a kidney transplant, because the successful addition of a pancreas does not jeopardize patient survival, may improve kidney survival, and will restore normal glycemia.
ADA RECOMMENDATIONS

- The pancreas transplant may be done simultaneous to, or subsequent to, a kidney transplant. Pancreas graft survival is better when done simultaneous to a kidney transplant.
ADA RECOMMENDATIONS

• In the absence of indications for kidney transplantation, pancreas transplantation should only be considered a therapy in patients who exhibit these three criteria:
  
• 1) a history of frequent, acute, and severe metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention;
Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society.

- Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.

- Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

ADA RECOMMENDATIONS

2) clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and

3) consistent failure of insulin-based management to prevent acute complications.
Indications for Pancreas Tx

- Type I diabetes + ESRD: **SPK 72 %**
- Type I diabetes + St.p. Kidney Tx: **PAK 17 %**
- Brittle type I diabetes ± rapidly progressing diabetic complications: **PA 7 %**
- St. p. pancreatectomy for benign disease: **PA with enteric drainage**
Pancreas Transplantation
Contraindications

- Advanced coronary artery disease
- Advanced peripheral vascular disease
- Malignancy
- Chronic (untreated) infection
- Obesity
- Type 2 diabetes mellitus
### 2007-2010 Pancreas Transplant Volumes

<table>
<thead>
<tr>
<th>Center</th>
<th>2007</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>INIM-TX1 IU/Riley</td>
<td>82</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>MNUM-TX1 Univ. of Minnesota</td>
<td>53</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>NEUN-TX1 Nebraska</td>
<td>49</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>WIUW-TX1 Wisconsin</td>
<td>40</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td>FLJM-TX1 Jackson Memorial</td>
<td>39</td>
<td>37</td>
<td>23</td>
</tr>
<tr>
<td><strong>OHCC-TX1 Cleveland Clinic</strong></td>
<td><strong>33</strong></td>
<td><strong>28</strong></td>
<td><strong>22</strong></td>
</tr>
<tr>
<td>PAPT-TX1 Univ of Pittsburgh</td>
<td>30</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td>AZMC-TX1 Mayo Clinic Hospital</td>
<td>29</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>OHOU-TX1 Ohio State Univ</td>
<td>28</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>ILNM-TX1 Northwestern Memorial</td>
<td>25</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>MDUM-TX1 Univ of Maryland</td>
<td>24</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>CASF-TX1 UCSF</td>
<td>20</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>MDJH-TX1 Johns Hopkins</td>
<td>20</td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>
Immunosuppression Simultaneous Pancreas-Kidney

- **Induction:** Basiliximab 20 mg Day 0, 4
- **Tacrolimus** 0.1-0.15 mg/kg/d
- **Mycophenolate** 1 gm BID
- **Steroid taper**
- **Goal** 12-hr trough FK levels 10-12 ng/ml
Immunosuppression
Solitary Pancreas Transplants

- RATG 1.0-1.5 mg/kg for ~ 4 to 5 mg/kg total
- Tacrolimus 0.1-0.15 mg/kg/d
- Mycophenolate 1 gm BID
- Steroid taper
- Goal 12-hr trough FK levels 12-15 ng/ml
Survival waiting vs transplanted


- 88%
- 82%
- 77%
2011 Update on Pancreas Transplantation: Comprehensive Trend Analysis of 25,000 Cases Followed Up Over the Course of Twenty-Four Years at the International Pancreas Transplant Registry (IPTR)
Angelika C. Gruessner
### CC Pancreas Transplants 1994-2009
Surgical complications in 236 transplants

<table>
<thead>
<tr>
<th>Complication</th>
<th>N</th>
<th>%</th>
<th>Graft loss</th>
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<tbody>
<tr>
<td>Re-operation</td>
<td>49</td>
<td>(20.5)</td>
<td>13 (26.5%)</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>2</td>
<td>(0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4</td>
<td>(1.7)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Infection</td>
<td>17</td>
<td>(7.1)</td>
<td>1 (5.8%)</td>
</tr>
<tr>
<td>Enteric leak</td>
<td>11</td>
<td>(4.6)</td>
<td>2 (18%) (27%)</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>(1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>9</td>
<td>(3.8)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Wound infxn/dehsc.</td>
<td>2</td>
<td>(0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>
Pancreas Transplantation
Secondary Complications

• **Nephropathy**
  - Reversal of diabetic changes in native kidneys-10 years (Fioretto, NEJM, 1998)
  - Influence in renal allografts

• **Neuropathy**
  - Possible benefit to peripheral sensory-motor neuropathy
  - ± Autonomic neuropathy

• **Retinopathy**
  - Amelioration of early stage lesions
  - Long-term follow-up necessary

• **Macroangiopathy**-Angio results, improved diastolic function etc.

• **QOL**


Robertson Paul Endocrinol Metab Clin N Am 2010 655-667
ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.
The Edmonton Protocol

- Sufficient number of high quality pancreatic islets
- Recipient selection
- Tailored immunosuppression
Introduction - UIC islet transplantation
Islet Transplantation for Brittle Type 1 Diabetes: The UIC Protocol

A. Gangemi, P. Salehi, B. Hatipoglu, J. Martellotto, B. Barbaro, J. B. Kuechle, M. Qi, Y. Wang, P. Pallan, C. Owens, J. Bui, D. West, B. Kaplan, E. Benedetti and J. Oberholzer, University of Illinois at Chicago, Chicago, IL

* Corresponding author: José Oberholzer,

29 Apr 2008 - Volume 8 - Issue 6 - pp 1250-1261
Long-Term Insulin Independence and Improvement in Insulin Secretion After Supplemental Islet Infusion Under Exenatide and Etanercept

Faradji, Raquel N.; Tharavanij, Thipaporn; Messinger, Shari; Froud, Tatiana; Pileggi, Antonello; Monroy, Kathy; Mineo, Davide; Baidal, David A.; Cure, Pablo; Ponte, Gaston; Mendez, Armando J.; Selvaggi, Gennaro; Ricordi, Camillo; Alejandro, Rodolfo

27 December 2008 - Volume 86 - Issue 12 - pp 1658-1665
Long-Term Insulin Independence and Improvement in Insulin Secretion After Supplemental Islet Infusion Under Exenatide and Etanercept

Faradji, Raquel N.; Tharavanij, Thipaporn; Messinger, Shari; Froud, Tatiana; Pileggi, Antonello; Monroy, Kathy; Mineo, Davide; Baidal, David A.; Cure, Pablo; Ponte, Gaston; Mendez, Armando J.; Selvaggi, Gennaro; Ricordi, Camillo; Alejandro, Rodolfo

27 December 2008 - Volume 86 - Issue 12 - pp 1658-1665
Reduced Progression of Diabetic Retinopathy After Islet Cell Transplantation Compared With Intensive Medical Therapy

Thompson, David M.1,5; Begg, Iain S.2; Harris, Claire1; Ao, Zilaing3; Fung, Michelle A.1; Meloche, R Mark3; Keown, Paul1; Meneilly, Graydon S.1; Shapiro, R Jean1; Ho, Stephen4; Dawson, Keith G.1; Ghofaili, Khalid Al1; Riyami, Loay Al1; Meethel, Mohammed Al1; Kozak, Sharon E.1; Tong, Suet On1; Warnock, Garth L.3

Volume 85(10), 27 May 2008, pp 1400-1405
Impact of Islet Transplantation on Diabetes Complications and Quality of Life

- Roberto Bassi & Paolo Fiorina

- 2011 Oct;11(5):355-63
Reduction in carotid intima-media thickness after pancreatic islet transplantation in patients with type 1 diabetes.


Long term graft function is the next challenge to overcome.
5 year follow up - Edmonton

Diagram A: % C-peptide positive vs. time (months)

Diagram B: % Insulin independence vs. time (months)

N = 47, 41, 29, 18, 11, 4, 4

*Diabetes* 54:2060–2069, 2005
Pathology of an Islet Transplant 2 Years After Transplantation: Evidence for a Nonimmunological Loss

Smith, R Neal; Kent, Sally C.; Nagle, Julie; Selig, Martin; Iafrate, A John; Najafian, Nader; Hafler, David A.; Auchincloss, Hugh; Orban, Tihamer; Caglieri, Enrico

Volume 86(1), 15 July 2008, pp 54-62
Islet Transplantation in Type 1 Diabetic Patients Using Calcineurin Inhibitor-Free Immunosuppressive Protocols Based on T-Cell Adhesion or Costimulation Blockade

Achieves 50% 5-year insulin independence


• Diabetes Care. 2012 Jul;35(7):1436-45
A: Rates of insulin independence after allogeneic islet infusion (islet transplant alone and IAK), annually after last infusion.

Barton F B et al. Dia Care 2012;35:1436-1445
International Trial of the Edmonton Protocol for Islet Transplantation

A.M. James Shapiro, M.D., Ph.D., Camillo Ricordi, M.D., Bernhard J. Hering, M.D., Hugh Auchincloss, M.D., Robert Lindblad, M.D., R. Paul Robertson, M.D., Antonio Secchi, M.D., Mathias D. Brendel, M.D., Thierry Berney, M.D., Daniel C. Brennan, M.D., Enrico Caglieri, M.D., Rodolfo Alejandro, M.D., Edmond A. Ryan, M.D., Barbara DiMercurio, R.N., Philippe Morel, M.D., Kenneth S. Polonsky, M.D., Jo-Anna Reems, Ph.D., Reinhard G. Bretzel, M.D., Federico Bertuzzi, M.D., Tatiana Froud, M.D., Raja Kandaswamy, M.D., David E.R. Sutherland, M.D., Ph.D., George Eisenbarth, M.D., Ph.D., Miriam Segal, Ph.D., Jutta Preiksaitis, M.D., Gregory S. Korbett, Ph.D., Franca B. Barton, M.S., Lisa Viviano, R.N., Vicki Seyfert-Margolis, Ph.D., Jeffrey Bluestone, Ph.D., and Jonathan R.T. Lakey, Ph.D.
• Long-Term Metabolic and Immunological Follow-Up of Nonimmunosuppressed Patients With Type 1 Diabetes Treated With Microencapsulated Islet Allografts


Endocrine Reviews

• Islets Transplanted in Immunoisolation Devices: A Review of the Progress and the Challenges that Remain

• Esther S. O’Sullivan, Arturo Vegas, Daniel G. Anderson, and Gordon C. Weir

• December 2011, 32(6):827–844
Strategies toward single-donor islets of Langerhans transplantation.

Shapiro, AM

16(6):627-631, December 2011
Expert Opinion on Biological Therapy

- Stem cell-based strategies for the treatment of type 1 diabetes Mellitus
  - Yujie Wen, Bo Chen & Suzanne T Ildstad
Chronic Pancreatitis

- Chronic pancreatitis, is a condition involving progressive inflammatory changes in the pancreas resulting in permanent structural damage, which can lead to impairment of exocrine and endocrine function
Chronic Pancreatitis: Surgical Treatment

- Surgery is indicated for pain control for patients failing medical therapy.
- Timing of the surgery is controversial.
Diabetes Treatment Options After Total Pancreatectomy

- Insulin replacement therapy with multiple daily injections or insulin pump
- Pancreas whole organ transplant for both endocrine and exocrine insufficiency
- Total pancreatectomy with simultaneous islet cell autotransplantation
HP249-MT Detail of the head during organ cleaning
HP249-MT during perfusion with exogenous enzymes.

The organ is slightly more extensible than the previous. After the collagenase has been delivered, a step that requires to minimize cuts in the parenkima, we do remove all tissue (including the area shown before and still visible here).
Detail of an islet of approximately 150 µm diameter.
Total pancreatectomy and islet autotransplantation for chronic pancreatitis.


Factors associated with islet yield and insulin independence after total pancreatectomy and islet cell autotransplantation in patients with chronic pancreatitis utilizing off-site islet isolation: Cleveland Clinic experience.

Johnston PC, Lin YK, Walsh RM, Bottino R……Faiman C
Hatipoglu BA

J Clin Endocrinol Metab.2015 May;100(5):1765-70.
Autologous Islet Transplantation

- Islet function full/partial at one year correlated with islet yield
  - <2500 IEQ/kg    n 64    32 %
  - 2501-5000 IEQ/kg n 65    79 %
  - > 5000 IEQ/kg   n 35    86 %
- Full function 7-27-63 % respectively
Long-Term Glycemic Control in Adult Patients Undergoing Remote vs. Local Total Pancreatectomy With Islet Autotransplantation.


Insulin independence among remote and local isolation cohorts
Total pancreatectomy and islet autotransplantation in chronic pancreatitis: Recommendations from PancreasFest

Melena D. Bellin a, Martin L. Freeman, Andres Gelrud,….. Michael R. Rickels, David C. Whitcomb, Jeffrey B. Matthews

the PancreasFest Recommendation Conference Participants

Pancreatology 14 (2014) 27e35
Evaluation should include:

A fasting glucose and hemoglobin A1c

Impairment in either fasting glucose (100-125 mg/dl) or hemoglobin A1c (5.7-6.4%) should be further evaluated by an oral glucose tolerance test.

Assessment of functional beta-cell mass should be considered as part of the evaluation and follow-up for TPIAT by serum C-peptide levels determined during either oral glucose or mixed meal tolerance testing.
Evaluation should include:

Intravenous glucose tolerance testing, arginine stimulation testing,

or

glucose-potentiated arginine testing for insulin and C-peptide responses

may provide more sensitive measures for beta cell mass, they can be performed in a research setting.
Metabolic assessment prior

The AUC glucose from the MMTT, fasting glucose, and HbA1c correlated inversely with the final product IEQ/kg.

Fasting glucose and peak stimulated C-peptide on MMTT ≥4 ng/mL. are significant predictors

Patient with a stimulated C-peptide ≥4 ng/ mL had 7.9 times the odds of receiving ≥2,500 IEQ/kg

Post-operative Follow Up

- Insulin infusion during and after transplantation
  Glycemic target: 60-126 mg/dl

- Converted to standardized sliding scale algorithm for insulin injections
  Daily diabetes review

- Diabetes education
  C-peptide: discharge, 2 week + 3 months
  MMTT: 6 + 12 months
  Clinic: 3, 6, 12 months, then yearly
Factors Predicting Outcomes After a Total Pancreatectomy and Islet Autotransplantation Lessons Learned From Over 500 Cases.
Chinnakotla, Srinath; Beilman, Gregory; Dunn, Ty; MD, MS; Bellin, Melena; Freeman, Martin; Radosevich, David; RN, PhD; Arain, Mustafa; Amateau, Stuart; MD, PhD; Mallery, J; Schwarzenberg, Sarah; Clavel, Alfred; Wilhelm, Joshua; Robertson, R; Berry, Louise; Cook, Marie; Hering, Bernhard; Sutherland, David; MD, PhD; Pruett, Timothy
DOI: 10.1097/SLA.0000000000001453

FIGURE 4. Insulin independence.
Sitagliptin Treatment After Total Pancreatectomy With Islet Autotransplantation: A Randomized, Placebo-Controlled Study.

Bellin MD, Beilman GJ, Dunn TB........ Berry KL, Hering BJ, Moran A

Am J Transplant. 2017 Feb;17(2):443-450
DPP-4 INHIBITOR THERAPY IN PATIENTS AFTER PANCREATIC TRANSPLANT.

- Ergin AB, Poggio E, Krishnamurthi V, Jaber T, Hatipoglu BA
Accuracy of Continuous Glucose Monitoring in Patients After Total Pancreatectomy with Islet Autotransplantation.

Forlenza GP, Nathan BM, Moran A, Dunn TB, Beilman GJ, Pruett TL, Kovatchev BP, Bellin MD

Successful Application of Closed-Loop Artificial Pancreas Therapy After Islet Autotransplantation.

Forlenza GP, Nathan BM, Moran AM, Dun TB, Beilman GJ, Pruett TL, Bellin MD

Am J Transplant. 2016 Feb;16(2):527-34.
Recurrent Hypoglycemic Episodes after TP-IAT

- 24 years old female post TP and hepatic AIT, who subsequently achieved insulin independence, developed episodes of post-exertional and fasting hypoglycemia eight months after surgery.

- Her hypoglycemic episodes was accompanied with fingersticks between 30-50 mg/dL with both neurologic and neuroglycopenic symptoms, which improved after food intake.

- She had hospital admissions and ED visit for hypoglycemic episodes, with blood glucose ranging between 34 and 45 mg/dL.
Spontaneous Hypoglycemia After Islet Autotransplantation for Chronic Pancreatitis.


From: Spontaneous Hypoglycemia After Islet Autotransplantation for Chronic Pancreatitis
J Clin Endocrinol Metab | Copyright © 2016 by the Endocrine Society
Table 2. Characteristics of patients attaining insulin independence and developing spontaneous hypoglycemia with timing and frequency

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age</th>
<th>Follow-up period (mos)</th>
<th>HbA1c</th>
<th>Frequency</th>
<th>Timing</th>
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<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>32</td>
<td>5.9</td>
<td>Every 1-2 weeks</td>
<td>Fasting, postprandial</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>51</td>
<td>5.7</td>
<td>3 times a week</td>
<td>Fasting, postprandial, exercise</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>36</td>
<td>5.4</td>
<td>3 times a week</td>
<td>Fasting</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>29</td>
<td>6.1</td>
<td>Twice a day</td>
<td>Fasting, postprandial, exercise</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>32</td>
<td>6.1</td>
<td>2-3 times/day</td>
<td>Fasting, exercise</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>16</td>
<td>5.1</td>
<td>Once a week</td>
<td>Fasting, postprandial</td>
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</table>
Table 3. Indicators of severe hypoglycemia and response to small frequent meals

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Incidence of BG &lt; 45 mg/dL</th>
<th>IAH Required help</th>
<th>Required glucagon rescue</th>
<th>ED/hospital admission</th>
<th>Limiting MV driving</th>
<th>Improvement with small frequent meals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (3-4 times; low blood glucose confirmed)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes (N/A (Limited oral intake; 12 hour tube feeding at night))</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (2 times; low blood glucose confirmed)</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tbody>
</table>
Defective Glucagon Secretion During Hypoglycemia After Intrahepatic But Not Nonhepatic Islet Autotransplantation


American Journal of Transplantation 2014; 14: 1880–1886
Comparison of glucagon responses at plasma glucose levels of 70, 60, and 50 mg/dl during stepped hypoglycemic, hyperinsulinemic clamps

Glucagon responses in the control group occurred by the time glucose levels reached 60 mg/dl and increased further by the time levels of 50 mg/dl were reached. In contrast, the TP/IAT-H group failed to have significant glucagon responses. However, glucagon responses were present in a subset of 5 recipients who had islets transplanted both in intrahepatic and non-hepatic (TP/IAT-H + NH) sites. See Results for statistics.
How should patients be followed after TPIAT?

- Lifelong monitoring for diabetes mellitus at least annually and should include self-monitored blood sugar, fasting blood glucose, and hemoglobin A1c.

- These patients may be followed for beta cell mass (C-peptide).

- Stimulatory tests (oral glucose or mixed meal tolerance tests) with measurement of glucose and C-peptide levels may also be considered to monitor islet function over time.
Every life deserves world class care.