Islet Transplantation

I. Description

Autologous islet transplantation, performed in conjunction with pancreatectomy, is proposed to reduce the likelihood of insulin-dependent diabetes. Moreover, allogeneic islet cell transplantation is being investigated as a treatment or cure for patients with type 1 diabetes.

Background

In autologous islet transplantation, during the pancreatectomy procedure, islet cells are isolated from the resected pancreas using enzymes, and a suspension of the cells is injected into the portal vein of the patient’s liver. Once implanted, the beta cells in these islets begin to make and release insulin. In the case of allogeneic islet cell transplantation, cells are harvested from the deceased donor’s pancreas, processed, and injected into the recipient’s portal vein. Up to 3 donor pancreas transplants may be required to achieve insulin independence. Allogeneic transplantation may be performed in the radiology department.

Chronic pancreatitis

Primary risk factors for chronic pancreatitis include toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive (the TIGAR-O classification system). Patients with chronic pancreatitis may experience intractable pain that can only be relieved with a total or near total pancreatectomy. However, the pain relief must be balanced against the certainty that the patient will be rendered an insulin-dependent diabetic. Autologous islet transplantation has been investigated as a technique to prevent this serious morbidity.

Type 1 diabetes

Allogeneic islet transplantation has been used for type 1 diabetes to restore normoglycemia and, ultimately, reduce or eliminate the long-term complications of diabetes such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Islet transplantation potentially offers an alternative to whole-organ pancreas transplantation. However, a limitation of islet transplantation is that 2 or more donor organs are usually required for successful transplantation, although
experimentation with single-donor transplantation is occurring. A pancreas that is rejected for whole-organ transplant is typically used for islet transplantation. Therefore, islet transplantation has generally been reserved for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management.

**Regulatory Status**

Islet cells are subject to regulation by the U.S. Food and Drug Administration (FDA), which classifies allogeneic islet cell transplantation as somatic cell therapy, requiring premarket approval. Islet cells also meet the definition of a drug under the federal Food, Drug, and Cosmetic Act. Clinical studies to determine safety and effectiveness outcomes of allogeneic islet transplantation must be conducted under FDA investigational new drug (IND) regulation. While at least 35 IND applications have been submitted to the FDA, no center has submitted a biologics license application.

**II. Policy**

Autologous pancreas islet transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

**III. Limitations/Exclusions**

Allogeneic islet transplantation is not covered for the treatment of type 1 diabetes as it is not known to be effective in improving health outcomes.

**IV. Administrative Guidelines**

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA’s [Precertification Request](#) and mail or fax the form as indicated along with the required documentation.

**A. Applicable codes:**

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>48160</td>
<td>Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells</td>
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<table>
<thead>
<tr>
<th>ICD-9 Procedure Codes</th>
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<tr>
<td>52.84</td>
<td>Autotransplantation of cells of islets of Langerhans</td>
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<tr>
<td>52.85</td>
<td>Allotransplantation of cells of islets of Langerhans</td>
</tr>
<tr>
<td>52.86</td>
<td>Transplantation of cells of islets of Langerhans, not otherwise specified</td>
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<table>
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<td>G0341</td>
<td>Percutaneous islet cell transplant, includes portal vein catheterization and infusion</td>
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B. Codes that do not meet payment determination criteria:

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>S2102</td>
<td>Transplant, islet cell tissue, allogeneic</td>
</tr>
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</table>

C. ICD-10 codes are provided for your information. These will not become effective until the ICD-10 compliance date.

<table>
<thead>
<tr>
<th>ICD-10-PCS</th>
<th>Description</th>
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<td>3E033U0</td>
<td>Percutaneous administration, peripheral vein, pancreatic islet cells, autologous</td>
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<td>3E0J3U0</td>
<td>Percutaneous administration, biliary and pancreatic tract, pancreatic islet cells, autologous</td>
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<tr>
<td>3E0J7U0</td>
<td>Administration via natural or artificial opening, biliary and pancreatic tract, pancreatic islet cells, autologous</td>
</tr>
<tr>
<td>3E0J8U0</td>
<td>Endoscopic administration via natural or artificial opening, biliary and pancreatic tract, pancreatic islet cells, autologous</td>
</tr>
</tbody>
</table>

V. Scientific Background

Chronic Pancreatitis

In 2012, Bramis and colleagues published a systematic review of studies on islet transplantation after total pancreatectomy in patients with chronic pancreatitis. (1) The investigators searched for studies reporting on patients who had been treated with total, subtotal or completion pancreatectomy followed by islet autotransplantation. Case series were included if they included more than 5 individuals and reported outcomes for consecutive patients. A total of 72 full-text articles were reviewed, and 5 studies were found to meet inclusion criteria. The postoperative insulin independence rate in the 5 studies ranged from 10% (mean follow-up=8 years) to 46% (mean follow-up=5 years). In the study with the longest follow-up, the insulin independence rate was 28% at 10 years. Two studies reported postoperative morphine use. In one study, patients reported a mean post-operative decrease in morphine use of 116 mg and in the other, a mean decrease of 55 mg of morphine was reported.

An earlier systematic review of studies on islet transplantation after pancreatectomy was published in 2011 by Dong and colleagues. (2) Studies were included regardless of design or sample size. After reviewing 84 studies, 15 observational studies were found to meet eligibility criteria. There were 11
studies of total pancreatectomy, 2 studies of partial pancreatectomy, and 2 studies that included both types of surgery. Sample sizes in individual studies ranged from 3 to 173 patients. Thirteen studies included patients with chronic pancreatitis, and 2 included patients with benign pancreatic tumors. The pooled 30-day mortality was 5% (95% confidence interval [CI]: 2 to 10%), and the cumulative mortality at 1 year (reported by 10 studies) was 4.9% (95% CI: 2.6 to 7.3%). In a pooled analysis of data from 14 studies, the rate of insulin dependence at last follow-up was 4.6 per 100 person years (95% CI: 1.53 to 7.62). The pooled rate of insulin independence at 1 year (5 studies) was 27% (95% CI: 21-33%) and at 2 years (3 studies) was 21% (95% CI: 16-27%).

Representative studies included in the systematic reviews or published more recently are described below:

A large single center series was reported by Sutherland and colleagues in 2012. (3) The study included 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation between February 1977 and September 2011. Fifty-three of the 409 patients (13%) were children between the ages of 5 and 18 years. Actuarial survival post-surgery was 96% in adults and 98% in children after 1 year and 89% in adults and 98% in children after 5 years. A total of 15.9% of patients experienced surgical complications requiring reoperation during the initial admission. The most common reason for reoperation was bleeding, occurring in 9.5% of patients. At 3 years, 30% of patients were insulin-independent (25% of adults and 55% of children). A survey of quality-of-life outcomes was initiated in October 2008; responses were available for 102 patients. At baseline, all 102 patients reported using narcotics for pain. At 12 months, the proportion of patients on narcotics decreased to 56% (n=32), and at 24 months, 41% of respondents (n=21) reported using narcotics.

In 2008, Webb and colleagues reported on 46 patients who had total pancreatectomy with immediate islet auto transplant. Twelve had periods of insulin independence for a median of 16.5 months (range, 2–63 months), and 5 remain insulin-independent. (4) Insulin requirements increased over the 10-year follow-up, as have HgA1c levels; however, all patients tested were C-peptide positive at their most recent assessment, and high fasting and stimulated C-peptide positive values recorded at 10 years after transplantation suggest significant graft function in the long term.

Type 1 Diabetes

In April 2004, TEC completed an evidence report on islet cell transplantation in type 1 diabetes in its capacity as an Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ). (5) The evidence report found that published data on clinical outcomes of islet-alone transplantation were limited by small patient numbers, few transplant centers, short duration of follow-up, and lack of standardized methods of reporting clinical outcomes. Rare, serious adverse events have occurred in patients given islet transplants; recent procedure modifications reportedly minimize risks of these adverse events. No procedure-related deaths, cytomegalovirus (CMV) infection, or post-transplantation lymphoproliferative disease (PTL) have been reported for islet-alone transplantation.
The 2008 report from the Collaborative Islet Transplant Registry (CITR), which collects and monitors data on allogeneic islet transplantation in North America, Europe, and Australia, had 325 adult recipients in their registry as of April 2008. (6) Three years after first infusion, 23% of islet-alone recipients were insulin-independent (defined as insulin-independent 2 or more weeks), 29% were insulin-dependent with detectable C-peptide, 26% had lost function, and 22% had missing data. Seventy percent achieved insulin independence at least once, 71% of whom were still insulin-independent 1 year later and 52% at 2 years. Factors that favored primary outcomes were higher number of islet infusions, greater number of total islet equivalents infused, lower pretransplant HbA1c levels, processing centers related to the transplant center, and larger islet size. The CITR published an updated report in 2012; the focus of the article was changes in outcomes over time. (7) The number of patients receiving islet transplants was 214 during 1999-2002, 255 between mid-2003-2006 and 208 from 2007-2010. A total of 575 of the 677 (85%) islet transplant recipients received islets only; the remainder underwent simultaneous kidney and islet transplants. In the 1999-2002 group, rates of insulin independence were 51% after 1 year, 36% after 2 years and 27% after 3 years. Rates for the 2007-2010 group were 66%, 55% and 44%, respectively. The incidence of clinically reportable adverse events in the first year after infusion decreased from 50-53% in 1999-2006 to 38% in 2007-2010. The rates of peritoneal hemorrhage or gallbladder infusion were 5.4% in 1999-2003 and 3.1% in 2007-2010. The authors did not report findings separately for the subset of patients who underwent islet-only transplants.

In 2011, Thompson and colleagues in Canada published findings from a prospective cross-over study of intensive medical therapy (pretransplant) versus islet cell transplantation in patients with type 1 diabetes. (8) The article reported on 45 patients; at the time of data analysis, 32 had received islet cell transplants. Median follow-up was 47 months pre-transplant and 66 months post-transplant. The overall mean HbA1c was 7.8% pretransplant and 6.7% post-transplant; this difference was statistically significant, p<0.001. In the 16 patients for whom sufficient data pre- and post-transplant were available on renal outcomes, the median decline in glomular filtration rate (GFR, mL/min/month) was -6.7 pretransplant and -1.3 post-transplant (p=0.01). Retinopathy was assessed using the International Scale, which categorizes nonproliferative diabetic retinopathy as mild, moderate, or severe. Retinopathy progressed in 10 of 82 (12%) eyes pretransplant versus 0 of 51 post-transplant (p<0.01). (The numbers of patients in the retinopathy analyses was not reported). The rate of change in nerve conduction velocity did not differ significantly between groups (exact numbers not reported). The authors noted that their finding of reduced microvascular complications after islet transplantation may be due, in part, to their choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil (MMF).

In 2012, Vantyghem and colleagues reported on 23 patients with type 1 diabetes who underwent islet transplantation; 14 had islet-only transplants and 9 had islet after kidney transplants. (9) Median HbA1c was 8.3% at baseline and 6.7% at 3 years. Ten of the 23 patients (43%) were insulin independent 3 years after islet transplantation. Findings were not reported separately for the islet-only transplant recipients.
Recent papers have highlighted research in the areas of islet cell regenerative therapy including stem-cell technology, encapsulating islets to protect them from the host immune system by a semipermeable capsule, and xenotransplantation. (10-13) In addition, novel immunosuppressive regimens using biologics have been discussed. (14)

Ongoing Clinical Trials

A comparison of strict glucose control with usual care at the time of islet cell transplantation (NCT01123122) (15): This is a single-center randomized controlled trial (RCT) comparing the impact of strict glucose control versus usual care prior to islet cell transplantation on outcomes in patients with type 1 diabetes. The primary study outcome is islet cell function 3 months post-transplantation. The estimated enrollment is 32 patients, and the estimated study completion date is September 2015.

A comparison of islet cell transplantation with medical therapy on the risk of progression of diabetic retinopathy and diabetic macular edema (NCT00853424) (16): This RCT is comparing islet cell transplantation to standard medical therapy in patients with diabetic eye disease. The primary outcome is progression of diabetic retinopathy or moderate visual loss. The estimated enrollment is 40 patients, and the estimated study completion date is June 2015.

Summary

Autologous islet transplantation is proposed in conjunction with pancreatectomy for patients with chronic pancreatitis. Although the published experience with autologous islet cell transplantation is limited, the procedure appears to significantly decrease the incidence of diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. In addition, this procedure is not associated with serious complications itself and is performed as an adjunct to the pancreatectomy procedure. Thus, this may be considered medically necessary.

The techniques for allogeneic islet cell transplants are evolving, and the impact on the net health outcome is still uncertain. Moreover, longer follow-up with larger numbers of patients is needed before conclusions can be drawn about the safety of allogeneic islet transplantation and its impact on diabetes mellitus and associated complications. Thus, this technology is not covered for patients with diabetes type 1.

Practice Guidelines and Position Statements

Guidance from the National Institute for Clinical Excellence (NICE), published in 2008, states that the evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus shows short-term efficacy with some evidence of long-term efficacy. (17) Evidence on safety shows that serious complications may occur, and the long-term immunosuppression required is also associated with risk of adverse events. The procedure is particularly indicated for patients with hypoglycemia unawareness or those already on immunosuppressive therapy because of renal transplantation. A 2008 update of guidance on autologous islet cell transplantation for improved glycemic control after pancreatectomy states that studies show some short-term efficacy, although
most patients require insulin therapy in the long term. Complications mainly result from the major surgery involved in pancreatectomy rather than from the islet cell transplantation. (18)

**Medicare National Coverage**

Effective October 1, 2004, Medicare will cover pancreatic islet transplantation in patients with type 1 diabetes participating in the context of a clinical trial sponsored by the National Institutes of Health. (19) Partial pancreatic tissue transplantation or islet transplantation performed outside the context of a clinical trial will continue to not be covered.

**VI. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawai‘i’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.
VII. References

9. Vantyghem MC, Raverdy V, Balavoine AS et al. Continuous glucose monitoring after islet transplantation in type 1 diabetes: an excellent graft function (beta-score greater than 7) is required to abrogate hyperglycemia, whereas a minimal function is necessary to suppress severe hypoglycemia (beta-score greater than 3). J Clin Endocrinol Metab 2012; 97(11):E2078-83.

