

Islet Transplantation

Effective: May 1, 2019

Next Review: March 2020

Last Review: April 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Islet cells are responsible for producing insulin, which is necessary for the regulation of blood glucose levels. Following islet transplantation, it is proposed that the beta cells in the transplanted islets will begin to make and release insulin.

MEDICAL POLICY CRITERIA

- I. Autologous pancreas islet cell transplantation may be considered **medically necessary** as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.
- II. Autologous pancreas islet cell transplantation for all other indications is considered **investigational**.
- III. Allogeneic and xeno islet cell transplantation for any diagnosis are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

CROSS REFERENCES

1. [Pancreas Transplant](#), Transplant, Policy No. 6

BACKGROUND

CHRONIC PANCREATITIS

Although the incidence of chronic pancreatitis is rising, it is still a relatively rare condition, affecting an estimated seven to eight new people out of every 100,000 people each year.^[1] Some 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 cell transplantation, also called islet autotransplantation (IAT), has been investigated as a technique to prevent this serious morbidity.

TYPE 1 DIABETES

Glucose control is a challenge for individuals with type 1 diabetes. Failure to prevent disease progression can lead to long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease.

ISLET TRANSPLANTATION

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.

Allogeneic islet cell transplantation is normally conducted as a stand-alone procedure among patients with type 1 diabetes. Islet cells, harvested from a deceased donor's pancreas, are processed and injected into the recipient's portal vein.

Allogeneic islet cell transplantation potentially offers an alternative to whole-organ pancreas transplantation to treat type 1 diabetes, restore normoglycemia and ultimately reduce or eliminate the long-term complications of diabetes, such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. However, a limitation of islet cell transplantation is that two or more donor organs are usually required for successful transplantation, and only pancreases rejected for whole-organ transplant are typically used for islet transplantation. Due to limited islet cell supply, allogeneic islet cell transplantation is recommended only for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management. In 2000, a modified immunosuppression regimen increased the success of allogeneic islet transplantation. This regimen was developed in Edmonton, Canada and is known as the "Edmonton protocol."

While most of the published research to date involves the transplantation of allogeneic human islet cells, there is also interest in xenotransplantation, using porcine islet cells.

REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Allogeneic islet cells are included in these regulations.

EVIDENCE SUMMARY

AUTOLOGOUS ISLET CELL TRANSPLANT AS AN ADJUNCT TO PANCREATECTOMY

Autologous islet cell transplantation as an adjunct to pancreatectomy or near total pancreatectomy among patients with chronic pancreatitis has been investigated since 1977. Since then, the experience has grown slowly with incremental improvements in the islet cell isolation process. The focus of this section is on systematic reviews.

Systematic Reviews

In 2015, Wu published a systematic review of studies on islet transplantation after total pancreatectomy for chronic pancreatitis.^[3] Studies could use any type of design but needed to include at least five patients or have a median follow-up of at least six months. Twelve studies with a total of 677 patients met the review's inclusion criteria. The mean age of the patients was 38 years and mean duration of pancreatitis was 6.6 years. A meta-analysis of the insulin independence rate at one year (five studies, 362 patients) was 28.4% (95% confidence interval [CI], 15.7% to 46.0%). At two years, the pooled insulin independence rate (three studies, 297 patients) was 19.7% (95% CI, 5.1% to 52.6%). The pooled 30-day mortality rate (11 studies) was 2.1% (95% CI, 1.2% to 3.8%). Long-term mortality data were not pooled.

In 2012, Bramis searched for studies reporting on patients who had been treated with total, subtotal or completion pancreatectomy followed by islet autotransplantation.^[4] Case series were included if they included more than five individuals and reported outcomes for consecutive patients. A total of 72 full-text articles were reviewed, and five studies were found to meet inclusion criteria. The postoperative insulin independence rate in the five studies ranged from 10% (mean follow-up of eight years) to 46% (mean follow-up of five years). In the study with the longest follow-up, the insulin independence rate was 28% at ten years. Two studies reported postoperative morphine use with a decrease in morphine use of 116 mg and 55 mg, respectively.

A 2011 systematic review by Dong included studies regardless of design or sample size.^[5] After reviewing 84 studies, 15 observational studies were found to meet eligibility criteria. There were 11 studies of total pancreatectomy, two studies of partial pancreatectomy, and two studies that included both types of surgery. Sample sizes in individual studies ranged from three to 173 patients. Thirteen studies included patients with chronic pancreatitis, and two 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 one year (reported by ten 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 one year (five studies) was 27% (95% CI: 21-33%)

and at two years (three studies) was 21% (95% CI: 16-27%).

ALLOGENEIC ISLET CELL TRANSPLANT FOR TYPE 1 DIABETES

Islet cell transplantation has also been investigated as a treatment for type 1 diabetes, particularly in patients with poor glucose control despite insulin therapy.

The principal outcomes associated with treatment of type 1 diabetes are improvement in overall mortality rate, and reductions in rates of diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease normally associated with type 1 diabetes. In order to understand the impact of islet cell transplantation for treatment of type 1 diabetes on these outcomes, well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as insulin treatment, are needed. Further, an understanding of any adverse treatment effects, particularly those associated with life-long immunosuppressant therapy, must be carefully weighed against any benefits associated with islet transplantation to understand the net treatment effect of this therapy.

Systematic Reviews

In 2015 Health Quality Ontario published a systematic review on islet transplantation for type 1 diabetes, and included one health technology assessment, 11 observational, nonrandomized clinical studies, one registry report, and four guidelines.^[6] There was a large degree of heterogeneity in patient populations, study design, and outcome measurement in the included studies. The reviewers reported that islet transplantation can improve blood sugar control and quality of life, and may reduce diabetic complications; however, the results were inconsistent between studies. Compared with insulin therapy, there were more adverse events with islet transplantation. The studies that were included that assessed health-related quality of life, secondary complications of diabetes, glycemic control, and adverse events were all ranked as low to very low quality, with two studies having high risk of bias. Therefore, uncertainty of the effectiveness of islet transplantation in type 1 diabetics still remains.

Randomized Controlled Trials

An open-label randomized controlled trial (RCT) was published by Lablanche in 2018 evaluating patients who had type 1 diabetes with severe hypoglycemia or in kidney transplant patients following transplantation.^[7] A total of 50 patients with severe hypoglycemia, hypoglycemia unawareness, or kidney grafts with poor glycemic control received immediate islet transplantation (n=25) or intensive insulin therapy followed by delayed islet transplantation (n=22). Median follow-up was six months for both groups. The primary end point was a composite score (β score) which has not been validated and which reflected fasting glucose, HbA1c level, C-peptide, and insulin independence. The proportion of patients with a modified β -score of 6 or higher at six months was 64% of patients in the immediate transplantation group and 0% in the control group ($p < 0.001$). Of note, few patients in the insulin group used continuous glucose monitoring or other technologies to monitor for hypoglycemia. At six months, insulin independence was achieved in 44% of patients in the immediate transplantation group ($N = 25$; $p = 0.0004$). After the entire cohort received islet transplantation, the one-year insulin independence rate was 59% ($N = 46$; $p < 0.0001$). Negative effects reported at 12 months included bleeding complications in 7% of patients and a decrease in median glomerular filtration rate from 90.5 mL/min to 71.8 mL/min in islet transplant patients who had not previously received a kidney graft and from 63.0 mL/min to 57.0 mL/min in islet transplant patients who had previously received a kidney graft. Trial

limitations included possible bias from open-label design as well as an inadequate follow-up period to demonstrate transplant durability.

Froud randomized 16 type 1 diabetes mellitus patients to evaluate cultured islet transplantation with or without tumor necrosis factor (TNF-alpha) blockade using Infliximab just prior to islet infusion.^[8] Insulin independence was achieved in 14 patients after one to two infusions, and was maintained in 11 patients after one year, and in six patients at 33 +/- 6-months without additional infusions. The authors reported no identifiable clinical benefit with the use of Infliximab, but concluded cultured human islet allografts produced results comparable to freshly transplanted islets including normalization of HBA1c. Further research in larger studies is needed to explore different immunosuppressive regimens.

Nonrandomized Studies

Holmes-Walker (2017) performed a within-subject paired comparison to examine the efficacy of insulin injections and islet transplantation to reduce hypoglycemia and glycemic variability in type 1 diabetes patients with severe hypoglycemia.^[9] Ten patients with type 1 diabetes were initially treated with insulin injections delivered as multiple daily injections (MDI). Patients then switched to continuous subcutaneous insulin infusion (CSII) and remained on CSII until islet transplantation. The authors completed a within-subject, paired comparison of MDI and CSII and CSII and 12 months post-islet transplantation. Following the switch from MDI to CSII, the average Edmonton Hypoglycemia Score (HYPOscore) reduced significantly, from 2028 to 1085 ($p < 0.05$), hypoglycemia events reduced significantly from 24 to 8 per patient-year ($p < 0.05$), the standard deviation of glucose and continuous overlapping net glycemic action using a four-hour interval (CONGA4) reduced significantly ($p < 0.05$), and HbA1c, mean glucose and median percent time hypoglycemic were unchanged. Twelve months post-islet transplantation, compared to CSII, there were significant reductions in HbA1c, median HYPO score, mean glucose, standard deviation of glucose, and CONGA4.

In 2015 Caiazzo assessed procedure-related complications on long-term outcome of islet transplantation in 26 patients with type 1 diabetes.^[10] Each patient had two to three intraportal islet infusions, performed surgically or under ultrasound guidance, within a three-month time frame. Complications included: bowel obstruction, biliary peritonitis and a major hepatic hematoma. The investigators reported no deaths or patient dropouts. Early complications occurred in nine of 68 procedures. Procedure-related complications negatively impacted graft function ($p = 0.009$) and was an independent negative predictor of long-term graft survival ($p = 0.033$) in multivariate analysis. The investigators concluded that even nonsevere complications occurring during islet transplantation, despite islet preparation method or transplantation method, significantly impair primary graft function and graft survival.

Moassesfar (2016) compared safety and efficacy of islet cell transplantation to pancreas transplantation at a center in the U.S.^[11] Sequential patients with type 1 diabetes had either an islet cell transplant ($n = 10$) or a pancreas transplant ($n = 15$). After one year, 90% of patients in the islet group and 93% of patients in the pancreas group were insulin independent. At three years, the proportion with insulin independence dropped to 70 % and 64%, respectively. The authors concluded that islet cell transplantation can produce similar outcome to pancreatic transplantation.

In 2013, Rickels reported on 12 patients with type 1 diabetes and severe hypoglycemia who had islet transplantation.^[12] Mean glycosylated hemoglobin decreased from $7.0\% \pm 0.3\%$ before the procedure to $5.6\% \pm 0.1\%$ after six to seven months ($p < 0.01$). All of the insulin sensitivity

measures were significantly less than normal before islet transplantation and not significantly different from normal after transplantation. Adverse events were not discussed.

In 2013, O'Connell reported on 17 patients who underwent islet transplantation for type 1 diabetes and severe hypoglycemia.^[13] The primary end point was the proportion of patients who had had an HbA1c less than 7% and no severe hypoglycemic events two months after the initial transplant. (Patients could have one or two infusions.) Fourteen of the 17 (82%) patients achieved the primary end point. Nine (53%) patients attained insulin independence for a median of 26 months. At the time of data analysis for this publication, six patients remained insulin independent. Most adverse events were related to immunosuppression. Seven of the 17 (41%) patients developed mild lymphopenia and one developed *Clostridium difficile* colitis; these all responded to treatment. Eight patients developed anemia shortly after transplant and one required a blood transfusion. Procedure-related complications included one partial portal vein thrombosis and three postoperative bleeds; two of the bleeds required transfusion. Patients were followed for different amounts of time; long-term follow-up data were not available for a consistent length of time.

In 2012, Vantighem reported on 23 patients with type 1 diabetes who underwent islet transplantation; 14 had islet-only transplants and nine had islet after kidney transplants.^[14] Median HbA1c was 8.3% at baseline and 6.7% at three years. Ten of the 23 patients (43%) were insulin independent three years after islet transplantation. Findings were not reported separately for the islet-only transplant recipients.

In 2011 Thompson reported on a prospective cross-over study of intensive medical therapy (pre-transplant) versus islet cell transplantation among 32 patients with type 1 diabetes.^[15] Following enrollment in the study, median follow-up was 47 months pre-transplant and 66 months post-transplant. Although improvements in HbA1c, retinopathy progression, and renal function were seen in the transplant group, small sample size and lack of treatment randomization limit interpretation of these findings. The authors also 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 2006, Shapiro reported on 36 patients with type 1 diabetes mellitus that had undergone islet transplantation.^[16] While short-term results were promising, insulin independence was generally not sustainable; only five patients were insulin-independent at two years. In a landmark study known as the Edmonton Protocol, seven consecutive patients achieved insulin independence following islet cell transplants from two to four donors on a glucocorticoid-free immunosuppressive regimen.^[17] However, 5-year outcomes from the first patients transplanted under the Edmonton protocol reported less than a 10% rate of insulin independence at five years, despite persistent graft survival as measured by C-peptide positivity (~80%).^[18] The authors noted that problems with glycemic lability and hypoglycemia, the primary indications for transplant, were corrected; however, no clear advantages for chronic complications of diabetes (e.g., peripheral neuropathy) were evident. Chronic complications related to standard immunosuppressive therapy led to the need to alter the protocol in 23% of patients, thus leading the authors to conclude that "safer immunosuppression associated with fewer side effects is needed." Complications and side effects related to both immunosuppression and the procedure itself are also reported to be more common than originally thought.^[19] The experience of the transplant center itself has a demonstrated effect on patient outcomes, with the more experienced centers reporting higher success rates.

Long-term results from the Edmonton Protocol were published by Brennan (2016), who reported that all seven of the original subjects continued to have some islet function more than ten years after the transplantation.^[20] One of the patients achieved insulin independence for eight years, but had graft failure 10.9 years after the first transplant. Of the other six subjects, three received an additional islet transplant, five were receiving insulin, and two were insulin-independent (with one taking liraglutide). None of the subjects had lymphoma, severe hypoglycemia, or opportunistic infections during follow-up.

Several other small case series have focused on identifying alternatives to current transplant techniques, studying encapsulated islet transplantation without immunosuppression,^[21] optimizing single versus multiple-donor transplantations,^[22] and comparing whole pancreas transplant to islet cell transplantation.^[23,24] Recent research also addresses islet-after-kidney transplantation.^[25] However, results from these studies should be interpreted with caution as the small sample sizes ($n \leq 66$), lack of randomized treatment allocation and/or appropriate comparison groups do not allow for ruling out chance as an explanation of findings.

Current non-randomized studies of allogeneic islet cell transplantation appear to suggest an initial benefit (such as a decline in HbA1c levels, for example) associated with the transplant. However, as a recent review of this therapy notes:^[26]

“[O]ne cannot be certain of the claim that partially failed islet transplantation leads to the use of less insulin and less hypoglycemia on a cause-effect basis. It could just as easily be that patients who enter transplant programs come under close clinical scrutiny by interested diabetologists who begin managing them more skillfully.”

Additional randomized controlled trials are needed to determine the strength and magnitude of potential benefits associated with this therapy and to isolate such the impact of such benefits from standard medical care.

REGISTRY DATA

Bretzel reported in 2007 data collected from the International Islet Transplant Registry from 1999-2004.^[27] Data were available for 458 human islet cell transplantations. At 1-year post transplant, patient survival was 97%, islet grafts were functioning in 82% of the cases, and insulin independence was achieved in 43% of the cases.

Founded in 2001 by the National Institute of Diabetes, Digestive and Kidney Diseases, the Collaborative Islet Transplant Registry (CITR) has been collecting information on allogeneic islet transplantation in North America, Europe, and Australia. The most recent peer-reviewed publication of CITR data was published in 2012.^[28] The update focused on changes in outcomes over time in 677 patients, all of whom received a transplant as of December 31, 2010 ($n=575$ islet-only; $n=102$ kidney+islet). Unfortunately, outcomes presented in this report were limited by considerable levels of missing data which increased with longer follow-up. The missing data were reported to be a mixture of unavailable medical records and data still pending entry into the registry.

The authors reported improved insulin independence at three years post-transplant, from 27% in the early era (1999–2002, $n = 214$) to 37% in the mid era (2003–2006, $n = 255$) and 44% in the most recent era (2007–2010, $n = 208$; $P = 0.006$ for years-by-era; $P = 0.01$ for era alone). However, not all recipients in the latter era had reached the three-year milestone at the time of this updated report. The need for islet reinfusion for loss of function of first graft by one-year

decreased significantly from 60-65% in 1999-2006 to 48% in 2007-2010 ($p < 0.01$). There was also a modest decrease in clinically reportable adverse events in the 2007-2010 era, 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 from the subset of patients who underwent islet-only transplants.

The Institute for Clinical and Experimental Medicine (IKEM), based in the Czech Republic, published results from a retrospective analysis of a registry of all patients receiving one or more allogeneic or autologous islet transplants from 2005 to 2010 ($n=15$ and $n=5$, respectively).^[29] Although islet function was documented in 11 of 15 and three of five patients, respectively, after 12 months (as indicated by C-peptide levels), only one patient receiving an allogeneic transplant was able to achieve independence from insulin beyond 12 months. The authors conclude that islet transplant may be best suited for high-risk recipients, as “routine clinical application is still hampered by the limited availability of usable organ transplants and viability of transplanted islets.”

Results from the above registry reports should be interpreted with caution as these registries are not reflective of the complete North American experience with islet transplants; not all transplant centers participated in each regional endeavor, nor is data complete for all those who do participate. Therefore, there may be inherent bias in the data. The focus on intermediate outcomes instead of long-term health outcomes, also limits interpretation of these findings.

XENOTRANSPLANTATION

Although there is research interest in porcine islets as an alternative and potentially unlimited source of islet cells, current data from human clinical trials is limited to three case series.

Matsumoto (2016) transplanted two doses of encapsulated neonatal porcine islets (approximately 5000IEQ/kg and 10,000IEQ/kg) twice in two groups of four patients each with type 1 diabetes.^[30] The two transplants were performed three months apart. One patient had a serious adverse event potentially related to the treatment, paralytic ileus, which was resolved with medication. While both groups had decreases in HbA1c, for the high dose group this difference remained significant at 600 days after the first transplant.

In 2011, Wang published results from a small clinical trial on the safety and feasibility of neonatal porcine islets (NPIs) in 22 patients in China.^[31] However, only six of the 22 patients were subsequently followed for more than two months, limiting conclusions about the long-term use of NPIs.

Also in 2011, Esquivel-Pérez published a report on 23 patients not on immunosuppression, transplanted with a porcine cell-filled device.^[32] Following an average of 5.7 years post-transplantation, the researchers reported that the patients with the lowest levels of antibodies were significantly more likely to report higher insulin dose reductions. However, not all patients were able to attain low levels of antibodies, for reasons not clearly known. Therefore, this report provides evidence for transplantation protocols but does not address the clinical utility of xenotransplantation.

Current literature has not directly addressed problems related to xenograft rejection and xenozoonosis (transmission of animal disease to humans).

PRACTICE GUIDELINE SUMMARY

In 2019, the American Diabetes Association (ADA) updated their position statement on comprehensive care for patients with type 1 diabetes.^[33,34] The statement includes a recommendation with a C rating stating that “Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes.” In addition, it states:

“Pancreas and islet cell transplantation have been shown to normalize glucose levels but require lifelong immunosuppression to prevent graft rejection and recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite aggressive glycemic management.”

SUMMARY

There is enough research to show that autologous islet cell transplantation is relatively safe and can reduce the chance of developing diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. Therefore, autologous islet cell transplantation may be considered medically necessary as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

There is not enough research to show that autologous islet cell transplantation can improve health outcomes for people with any other conditions. Therefore, autologous pancreatic islet cell transplantation for all other indications is considered investigational.

Although there is research interest in porcine islets (xeno islet cells) as a source of islet cells and allogeneic transplantation, there is not enough research to show that xenotransplantation or allogeneic transplantation is safe and effective, and there are no clinical guidelines based on research that recommend xenotransplantation or allogeneic transplantation. Therefore, xeno islet cell transplantation and allogeneic islet transplantation for any diagnosis are considered investigational.

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35. BlueCross BlueShield Association Medical Policy Reference Manual "Islet Transplantation." Policy No. 7.03.12

CODES

Codes	Number	Description
CPT	48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islets
	48999	Unlisted procedure, pancreas
HCPCS	G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion
	G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
	G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion
	S2102	Islet cell tissue transplant from pancreas; allogeneic

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