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Medical Policy Manual

Topic: Pancreas Transplant

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Section: Transplant

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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

Transplantation of a normal pancreas is a treatment method for patients with diabetes mellitus. Pancreas transplantation can restore glucose control, and is intended to prevent, halt, or reverse the secondary complications of insulin dependent Type 1 diabetes mellitus (IDDM). Achievement of insulin independence with resultant decreased morbidity and increased quality of life is the primary health outcome of pancreas transplantation. While pancreas transplantation is generally not considered a life-saving treatment, in a small subset of patients who experience life-threatening complications from IDDM, pancreas transplantation could be considered life-saving. In addition to the immune rejection issues common to all allograft transplants, autoimmune destruction of beta cells has been observed in the transplanted pancreas, presumably from the same mechanism responsible for type 1 diabetes.[1]

Pancreas transplantation occurs in several different scenarios such as:

1. Type 1 diabetic patient with renal failure who may receive a cadaveric simultaneous pancreas/kidney transplant (SPK)
2. Type 1 diabetic patient who may receive a cadaveric or living-related pancreas transplant after a kidney transplantation (pancreas after kidney, i.e., PAK)
3. Non-uremic type 1 diabetic patient with specific severely disabling and potentially life-threatening diabetic problems who may receive a pancreas transplant alone (PTA).

Pancreas transplant alone (PTA) has also been investigated in patients following total pancreatectomy for chronic pancreatitis. The experience with SPK transplants is more extensive than that of other transplant options.

The approach to retransplantation varies according to the cause of failure. Surgical/technical complications such as venous thrombosis are the leading cause of pancreatic graft loss among diabetic patients. Graft loss from chronic rejection may result in sensitization, increasing both the difficulty of finding a cross-matched donor and the risk of rejection of a subsequent transplant. Each center has its own guidelines based on experience; some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

Note: Islet cell transplantation is considered separately in Medical Policy, Transplant, No. 13.

MEDICAL POLICY CRITERIA

I. Candidates for all types of pancreas transplant must meet all of the following criteria:

   A. Adequate cardiopulmonary status

   B. Documentation of patient compliance with medical management

II. The following may be considered **medically necessary** if <u>both</u> of the above criteria are met:

   A. A combined pancreas-kidney transplant in diabetic patients with uremia.

   B. Pancreas transplant after a prior kidney transplant in patients with IDDM.

   C. Pancreas transplant alone in patients with documentation of one or both of the following conditions, which persist in spite of optimal medical management:

      1. Severely disabling and potentially life-threatening hypoglycemia unawareness as evidenced by chart notes or emergency room visits; OR

      2. Potentially life-threatening labile diabetes as evidenced by documentation of erratic blood glucose levels and hemoglobin A1c equal to or greater than 8% or hospitalization for diabetic ketoacidosis.

   D. Pancreas retransplantation after one failed primary pancreas transplant may be considered **medically necessary**.

III. Pancreas transplantation that does not meet the above criteria is considered **not medically necessary.**

POLICY GUIDELINES

Multiple Transplants

Although there are no standard guidelines regarding multiple pancreas transplants, the following information may aid in case review:

- If there is early graft loss resulting from technical factors (e.g., venous thrombosis), a retransplant may generally be performed without substantial additional risk.
- Long-term graft losses may result from chronic rejection, which is associated with increased risk of infection following long-term immunosuppression, and sensitization, which increases the difficulty of finding a negative cross-match. Some transplant centers may wait to allow reconstitution of the immune system before initiating retransplant with an augmented immunosuppression protocol.

SCIENTIFIC EVIDENCE

Literature Appraisal

Pancreas After Kidney Transplant (PAK)[2]

PAK transplantation allows the uremic patient the benefits of a living-related kidney graft, if available, and the benefits of a subsequent pancreas transplant that is likely to result in improved quality of life compared to a kidney transplant alone. Uremic patients for whom a cadaveric kidney graft is available but a pancreas graft is not simultaneously available benefit similarly from a later pancreas transplant. Based on international pancreas registry data, at 5 years' post-transplant, the patient survival rate after PAK is 83%.[3]

In 2012, Bazerbachi and colleagues reviewed a single center's experience with PAK and synchronous pancreas-kidney (SPK) transplantations.[4] Between 2002 and 2010, 172 pancreas transplants were performed in diabetic patients; 123 SPK and 49 PAK. The median length of time between kidney and pancreas transplantation in the PAK group was 4.8 years. Graft and patient survival rates were similar in the 2 groups. Death-censored pancreas graft survival rates for SPK and PAK were 94% and 90% at 1 year, 92% and 90% at 3 years, and 85% and 85% at 5 years (all respectively, p=0.93). Patient survival rates (calculated beginning at the time of pancreas transplantation) in the SPK versus PAK groups were 98.3% and 100% after 1 year, 96.4% and 100% after 3 years, and 94.2% and 100% after 5 years (all respectively, p=0.09).

In 2009, Fridell and colleagues reported a retrospective review (n=203) of a single center's experience with PAK and SPK since 2003, when current induction/tacrolimus immunosuppressive strategies became standard.[5] Of the cases studied, 61 (30%) were PAK and 142 (70%) were SPK. One-year patient survival rates were 98% and 95% (PAK and SPK, respectively; p=0.44). Pancreas graft survival rates at 1 year were observed to be 95% and 90%, respectively (p=0.28). The authors conclude that in the modern immunosuppressive era, PAK should be considered as an acceptable alternative to SPK in candidates with an available living kidney donor.

In 2009, Kleinclauss and colleagues retrospectively examined data from diabetic kidney transplant recipients (n=307) from a single center and compared renal graft survival rates in those who subsequently received a pancreatic transplant to those who did not.[6] The comparative group was analyzed separately depending on whether they were medically eligible (KTA-E) for pancreas transplant, but chose not to proceed for financial or personal reasons, or were ineligible (KTA-I) for medical reasons. The KTA-I (n=57) group differed significantly at baseline from both the PAK group (n=175) and the KTA-E group (n=75) with respect to age, type of diabetes and dialysis experience; kidney graft survival rates were lower than either of the other groups, with 1-, 5-, and 10-year rates of

75%, 54%, and 22%, respectively (p<0.0001). The PAK and KTA-E groups were similar in age, race, type of diabetes, and dialysis experience. The authors compared 1-, 5-, and 10-year kidney graft survival rates in PAK patients with those in the KTA-E group: 98%, 82%, and 67% versus 100%, 84%, and 62%, respectively, and concluded that the subsequent transplant of a pancreas after a living donor kidney transplant did not adversely affect patient or kidney graft survival rates.

Pancreas Transplant Alone (PTA)[2]

PTA graft survival has improved in recent years. According to international registry data 1--year graft function increased from 51.5% in 1987-1993 to 77.8% in 2006-2010 (p<0.0001).[3] One-year immunologic graft loss remains higher (6%) after PTA than PAK (3.7%) or SPK (1.8%). In carefully selected IDDM patients with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile diabetes that persists despite optimal medical management, the benefits of PTA were judged to outweigh the risk of performing pancreas transplantation with subsequent immunosuppression. The majority of patients undergoing PTA are those with either hypoglycemic unawareness or labile diabetes. However, other exceptional circumstances may exist where non-uremic IDDM patients have significant morbidity risks due to secondary complications of diabetes (e.g., peripheral neuropathy) that exceed those of the transplant surgery and subsequent chronic immunosuppression. Because there is virtually no published evidence regarding outcomes of medical management in this very small group of exceptional diabetic patients, it is not possible to generalize about which circumstances represent appropriate indications for pancreas transplantation alone. Case-by-case consideration of each patient's clinical situation may be the best option for determining the balance of risks and benefits.

Noting that nephrotoxic immunosuppression may exacerbate diabetic renal injury after PTA, Scalea et al reported a single institutional review of 123 patients who received 131 PTA for development of renal failure.[7] Mean graft survival was 3.3 years (range, 0–11.3), and 21 patients were lost to follow-up. Mean estimated glomerular filtration rate (eGFR) was 88.9 pre-transplantation versus 55.6 post-transplantation, with mean follow-up of 3.7 years. All but 16 patients had a decrease in eGFR, and mean decrement was 32.1 mg/min/1.73. Thirteen developed end-stage renal disease, which required kidney transplantation at a mean of 4.4 years. The authors suggested that patients should be made aware of the risk and only the most appropriate patients offered PTA. Future updates of this policy will continue to follow this clinical topic.

Simultaneous Pancreas/Kidney Transplant (SPK)

According to international registry data through 2005, recent 5-year graft survival rates for SPK transplants are 72% for the pancreas and 80% for the kidney.[8] Ten-year graft survival rates have reached almost 60% for SPK transplants.

In 2010, Mora and colleagues described the long-term outcome of 12 patients 15 years following SPK transplant.[9] Metabolic measures of glucose control were measured at 1, 5, 10, and 15 years following the procedure. Of this subset of patients, 6 (50%) had non-diabetic glucose challenge tests. Basal serum insulin levels declined over this period as well, from 24 mU/L to 16 mU/L at 1 and 15 years, respectively. The authors concluded that in a select group of patients whose pancreatic graft continued to function after 15 years, some glycemic control continued, albeit in a diminished fashion. It should be noted that this represented a small fraction of the 367 patients receiving the SPK transplant at this single center (12 of 367 SPK; 3.3%). The number of allograft survivals at 5 or more, and 10 or more years in this study was 43 (11.7%) and 28 (7.6%), respectively.

The improved glycemic control that may occur in SPK transplant patients, principally in those with labile disease while on medical therapy alone, is purported to reduce risk of complications from the diabetic disease. In 2009, Davenport and colleagues published results of a registry review (n=58) on cardiovascular risk factors in an Irish study of SPK transplant recipients.[10] Glycosylated hemoglobin values fell from a mean of 8.1 to 5.2 ($p<0.0001$) from pre-transplant levels. Similar statistically significant declines were seen in total cholesterol, triglycerides, and creatinine. Systolic and diastolic blood pressures were likewise improved but with a greater range of pre- and post-transplant variability. These endpoints are commonly accepted as surrogates for cardiovascular risk. The authors compared both a surgical method (bladder vs. enteric drainage) and mode of immunosuppression (cyclosporine vs. tacrolimus) on changes to blood pressure and cholesterol. No significant differences were found in either measure based on surgical drainage method, nor did immunosuppressive therapy have an impact on blood pressure reduction. Cholesterol reduction was greater in the cyclosporine than the tacrolimus group (-1.3 to -0.2, respectively), favoring the less contemporary strategy. The authors noted that this was in contrast to other recently published studies favoring both enteric drainage and tacrolimus. While this single arm study suggested beneficial cardiovascular effects from transplant, other factors such as rejection rates were more likely to influence the conditions under which transplantations took place.

In 2011, Sampaio and colleagues published an analysis of data from the United Network for Organ Sharing (UNOS) database.[11] The investigators compared outcomes in 6,141 patients with type 1 diabetes and 582 patients with type 2 diabetes who underwent SPK between 2000 and 2007. In adjusted analyses, outcomes were similar in the two groups. After adjusting for other factors such as body weight; dialysis time; and cardiovascular comorbidities, type 2 diabetes was not associated with an increased risk of pancreas or kidney graft survival or mortality compared to type 1 diabetes.

Pancreas Retransplantation[12]

According to data posted by the OPTN, for the period 1997-2004, patient survival rates were similar for primary transplants and repeat transplants.[13] For example, the 1-year survival rate among 1,216 individuals who had a primary pancreas transplant was 94.0% (95% confidence interval [CI]: 92.6 to 95.3%), and the 1-year survival rate among 255 patients with a repeat pancreas transplant was 95.6% (95% CI: 92.7-98.5%). Three-year survival rates were 89.5 (95% CI: 87.8 to 91.2%) for 1,004 patients with primary transplants and 89.7% (95% CI: 85.9% to 93.5%) for 225 patients with repeat transplants. One-year graft survival rates were 78.2% (95% CI: 76.0 to 80.5%) after primary pancreas transplants and 70.4% (95% CI: 64.8 to 76.0%) after repeat transplants.

Data were similar for patients receiving combined kidney/pancreas transplants, but follow-up data were only available on a small number of patients who had repeat kidney/pancreas transplants, so estimates of survival rates in this group were imprecise. Three-year patient survival rates were 90% (95% CI: 89.0 to 91.0%) for 2,902 patients who had a primary transplant and 79.9% (63.8 to 95.9%) for 26 patients who had a repeat transplant.

In 2013, Buron and colleagues reported on their experience with pancreas retransplantation in France and Geneva.[14] Between 1976 and 2008, 568 pancreas transplants were performed at 2 centers, including 37 repeat transplants. Patient survival after a repeat pancreas transplant was 100% after 1 year and 89% after 5 years. Graft survival was 64% at 1 year and 46% at 5 years. Among the 17 patients who underwent a second transplant in a later time period i.e., between 1995 and 2007, graft survival was 71% at 1 year and 59% at 5 years. In this more recently transplanted group, graft survival rates were similar to primary pancreas transplants which was 79% at 1 year and 69% at 5 years.

Studies for pancreatic retransplantation are limited to retrospective reviews and non-randomized feasibility studies. The evidence for graft and patient survival following the first retransplantation of the pancreas following PAK, PTA, or SPK transplantation has shown outcomes similar to primary transplantation.[13,15-18] No clinical trials were found that reported survival outcomes following more than 1 retransplantation.

HIV+ Transplant Recipients

In March 2009, the Organ Procurement Transfer Network (OPTN) revised its policies on HIV status in recipients. It reiterated an earlier statement that "A potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is documented contraindication to transplantation based on local policy."[19]

In 2009, the Clinical Practice Committee of the American Society of Transplantation and the American Society of Transplant Surgeons proposed that the presence of AIDS could be considered a contraindication to kidney transplant unless the following criteria were present.[20] These criteria may be extrapolated to other organs:

- CD4 count >200 cells/mm-3 for ≥6 months
- HIV-1 RNA (i.e., viral load) undetectable ≥ 3 months
- On stable anti-retroviral therapy ≥3 months
- No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioses mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
- Meeting all other criteria for transplantation

A retrospective analysis of all deceased donor pancreas transplants performed in the U.S. between 1988 and 1999 revealed that since the mid-1990's allograft half-lives ranged from eight to nine years for PTA transplants to nearly 13 years for SPK transplants.[21] The data indicates that insulin-independence with functioning grafts can been achieved for longer than 20 years.

Age

Several 2011 studies addressed pancreas transplantation in individuals 50 years of age or older. Afaneh and colleagues reviewed data on 17 individuals at least 50-years-old and 119 individuals younger than 50 who had a pancreas transplant at a single institution in the U.S.[22] The two groups had similar rates of surgical complications, acute rejection and non-surgical infections. Overall patient survival was similar. Three- and 5-year survival rates were 93% and 90% in the younger group and 92% and 82% in the older group. Schenker and colleagues in Germany compared outcomes in 69 individuals at least 50-years-old and 329 individuals younger than 50 years who had received a pancreas transplant.[23] Mean duration of follow-up was 7.7 years. One-, 5-, and 10-year patient and graft survival rates were similar in the two groups. For example, the 5-year patient survival rate was 89% in both groups. The 5-year pancreas grant survival rate was 76% in the older group and 72% in the younger group. The authors of both studies, as well as the authors of a commentary accompanying the Schenker article,[24] agreed that individuals age 50 years and older are suitable candidates for pancreas transplantation.

Clinical Practice Guidelines

The American Diabetes Association Position Statement made the following recommendations on kidney and pancreas transplantation for patients with type 1 diabetes:[25]

- For patients with imminent or established end-stage renal disease who have had or plan to have a kidney transplant, simultaneous or subsequent pancreas transplantation should be considered an acceptable therapeutic alternative to continued insulin therapy.
- Pancreas-alone transplantation should only be considered in patients who exhibit the following: 1) history of frequent, acute, and severe metabolic complications (hypoglycemia, marked hyperglycemia, ketoacidosis) requiring medical attention; 2) clinical and emotional problems with exogenous insulin therapy that are so sever as to be incapacitating; and 3) consistent failure of insulin-based management to prevent acute complications.

Summary

No randomized controlled trials compared any form of pancreas transplant to insulin therapy. The literature, consisting primarily of case series and registry data, demonstrated graft survival rates and immunosuppressive therapy risks for primary or first repeat pancreas transplant to be comparable to other solid organ transplants. Therefore, medical necessity may be considered established for these procedures in patients who meet the medical necessity criteria. These procedures are considered not medically necessary when the criteria are not met.

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CROSS REFERENCES

Islet Cell Transplantation, Transplant, Policy No. 13

CODES	NUMBER	DESCRIPTION
CPT	48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
	48551	Backbench standard preparation of cadaver donor pancreas allograft prior to

CODES	NUMBER	DESCRIPTION
		transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomosis from the iliac artery to superior mesenteric artery and to splenic artery
	48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
	48554	Transplantation of pancreatic allograft
HCPCS	S2065	Simultaneous pancreas kidney transplantation
	S2152	Solid organs(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition