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Surgical Complications Requiring Early Relaparotomy After Pancreas Transplantation

A Multivariate Risk Factor and Economic Impact Analysis of the Cyclosporine Era

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Objectives
To study significant surgical complications requiring early (≤3 months posttransplant) relaparotomy (relap) after pancreas transplants, and to develop clinically relevant surgical and peritransplant decision-making guidelines for preventing and managing such complications.

Summary Background Data
Pancreas grafts are still associated with the highest surgical complication rate of all routinely transplanted solid organs. However, the impact of surgical complications on morbidity, hospital costs, and graft and patient survival rates has not been analyzed in detail to date.

Methods
We retrospectively studied surgical complications requiring relap in 441 consecutive cadaver, bladder-drained pancreas transplants (54% simultaneous pancreas and kidney [SPK]; 22% pancreas after kidney [PAK]; 24% pancreas transplant alone [PTA]; 37% retransplant). Outcome and hospital charges were analyzed separately for recipients with *versus* without reoperation.

Results
The overall relap rate was 32% (SPK, 36%; PAK, 25%; PTA, 16%; $p = 0.04$). The most common causes were intraabdominal infection and graft pancreatitis (38%), pancreas graft thrombosis (27%), and anastomotic leak (15%). Perioperative relap mortality was 9%; transplant pancreatectomy was necessary in 57% of all recipients with one or more relaps. The pancreas graft was lost in 80% of recipients with *versus* 41% without relap ($p < 0.0001$). Patient survival rates were significantly lower ($p < 0.05$) for recipients with *versus* without relap. By multivariate analysis, significant risk factors for graft loss included older donor age (SPK, PAK), retransplant (PAK), relap for infection (SPK, PAK), and relap for leak or bleeding (PAK). For death, risk factors included older recipient age (SPK, PAK),

retransplant (SPK, PAK), relap for thrombosis (PAK), relap for infection or leak (SPK), and relap for bleeding (PTA).

Conclusions

Posttransplant surgical complications requiring relap were frequent, resulted in a high rate of pancreas (SPK, PAK, PTA) and kidney (SPK, PAK) graft loss, and had a major economic impact ($p = 0.0001$). Complications were associated with substantial perioperative mortality and decreased patient survival rates. The focus must therefore shift from graft salvage to preservation of the recipient's life once a pancreas graft-related complication requiring relap occurs. Thus, the threshold for pancreatectomy should be low. In this context, acceptance of older donors and recipients must be reconsidered.

For type I insulin-dependent diabetic patients, solid organ pancreas transplantation is currently the only treatment option that routinely and consistently restores continuous normoglycemia and normalizes long-term hemoglobin A_{1C} levels.[1] But despite a large pool of potential recipients, widespread application of pancreas transplantation has been hampered by a substantial rate of nonimmunologic graft failure. According to a recent United Network for Organ Sharing (UNOS) report, 11% to 21% of all pancreas grafts are lost because of surgical complications (*e.g.*, intraabdominal infection, vascular graft thrombosis, anastomotic leak).[2]

Unfortunately, we have no detailed data on the impact of these complications on peritransplant morbidity and mortality, on long-term patient survival, or on economic parameters. All of these are extremely relevant issues, because transplantation of a pancreas is not considered life-saving; rather, it has been touted as a procedure done primarily to improve quality of life.[3] Thus, detailed and *separate* outcome analyses, for pancreas transplants with *versus* without complications, are of paramount importance. Such analyses will also help transplant centers facing mounting economic constraints, ongoing reorganization of the health-care sector, and increasing scrutiny by public and private health insurance carriers.

In our retrospective study, we reviewed the most serious surgical complications—in other words, those requiring reoperation during the early posttransplant period (≤3 months posttransplant). Our purpose was threefold: 1) to study the spectrum of surgical complications pancreas transplant surgeons need to manage; 2) to assess the perioperative mortality and the implications for long-term graft and patient survival of these complications; and 3) to determine their economic impact. Given the multitude of donor and recipient risk factors that can potentially affect pancreas transplant outcome,[4–7] we applied multivariate analysis methods to all three recipient categories (all routine at the University of Minnesota): simultaneous pancreas and kidney transplants (SPK) for uremic or preuremic recipients; pancreas after kidney transplants (PAK) for nonuremic recipients with a stable previous kidney graft; and pancreas transplants alone (PTA) for nonuremic recipients with adequate native kidney function.

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PATIENTS AND METHODS

Study Population

Our study included all 441 consecutive cadaver, whole organ, bladder-drained pancreas transplants done at the University of Minnesota between July 1, 1986, and December 31, 1994, for type I insulin-dependent diabetic recipients. Of these 441 transplants, 236 (54%) were SPK, 101 (22%) were PAK, and 104 (24%) were PTA. Table 1 lists recipient demographics, donor age, and preservation time for each of these recipient categories. All prospective pancreas recipients routinely underwent a thorough cardiac evaluation according to an algorithm that included perfusion scintigraphy, cardiac ultrasonography, coronary angiography, and coronary revascularization (when indicated).[8,9]

Donor and Recipient Operation

The technical aspects of the transplant procedure have been previously described in detail.[6,10] In the donor operation, a nasogastric tube was advanced across the pylorus into the donor duodenum. It was used to flush the duodenum with 250 mL of normal saline solution containing cefazolin sodium (4000 mg/L), amikacin (2000 mg/L), and amphotericin B (200 mg/L). In the recipient operation, the graft was placed intraperitoneally through a midline incision. The graft was revascularized using either the recipient's iliac vasculature or the distal inferior vena cava and lower abdominal aorta. A duodenocystostomy was created, either hand-sewn (two-layer technique) or with the EEA stapler,[11] between the antimesenteric lateral

Table 1. RECIPIENT DEMOGRAPHICS, DONOR AGE, AND PRESERVATION TIME (BY RECIPIENT CATEGORY)

	SPK (n = 236)	PAK (n = 101)	PTA (n = 104)
% Male/female	55/45	42/58	24/76
Mean age at transplantation (yr) (±SD; range)	38.1 (±7.4; 22–57)	36.6 (±7.2; 22–59)	33.9 (±7.8; 11–59)
Mean duration of diabetes (yr) (±SD; range)	24.8 (±6.7; 10–44)	26.1 (±6.3; 13–40)	20.2 (±8.1; 2–43)
% Retransplants	8	37	30
% Pretransplant dialysis	60	0	0
Mean donor age (yr) (±SD; range)	33.6 (±14.7; 4–68)	30.4 (±14.3; 14–67)	30.1 (±13.9; 5–65)
Mean preservation time (hr) (±SD; range)	18.1 (±5.2; 4–38)	17.2 (±5.1; 5–30)	17.6 (±4.7; 2–33)

SPK = simultaneous pancreas-kidney transplant; PAK = pancreas after kidney transplant; PTA = pancreas transplant alone.

aspect of the donor duodenum and the posterosuperior aspect of the bladder dome. In SPK recipients, the kidney was also placed intraperitoneally and the ureteroneocystostomy was done using the extravesical Leadbetter-Politano technique. Before the recipient operation was completed, the abdominal cavity was irrigated with at least 4 L of irrigating solution containing cephalothin sodium (1000 mg/L) and amphotericin B (20 mg/L).

Immunosuppression

All recipients were started during surgery on prednisolone (2 mg/kg/day on day 0 to day 2; tapered to 1 mg/kg/day by day 7, to 0.5 mg/kg/day by day 15, and to 0.1 mg/kg/day by 6 months posttransplant). Azathioprine was started at 2.5 mg/kg intravenously during surgery and continued at 2.5 mg/kg/day orally indefinitely (adjusting the dose for white blood cell count and concurrent infections). Before August 1992, all recipients received a 7- to 14-day induction course of Minnesota antilymphocyte globulin; since then, antithymocyte globulin (Upjohn, Kalamazoo, MI) (both at 20 mg/kg/day intravenously) or OKT3 (Ortho Biotech, Raritan, NJ) (5 mg/day intravenously) was used. Cyclosporin A (CsA) was started at 8 mg/kg/day orally on day 5 (or 3 mg/kg/day intravenously in a continuous infusion, for recipients not yet on oral medications). For all recipients, maintenance therapy consisted of prednisone, azathioprine, and CsA. CsA levels were adjusted during induction and maintenance therapy to achieve whole blood levels of 200 to 250 ng/mL, using high-pressure liquid chromatography. Recipients with tacrolimus-based immunosuppression were not included in this study.

All pancreas and kidney rejection episodes were treated by recycling the prednisone taper (starting at 2 mg/kg/day orally and then tapering to the prerejection steroid dose within 14 days) or by intravenous steroid-pulse therapy (methylprednisolone 500 mg/day for 3 days). Most pancreas rejection episodes, histologically severe kidney rejection episodes (because of the high incidence of steroid resistance), and steroid-resistant kidney episodes were treated with a 7- to 10-day course of antilymphocyte globulin, antithymocyte globulin (both at 20 mg/kg/day intravenously), or OKT3 (5 mg/day intravenously).

Pancreas Rejection

Pancreas rejection episodes were diagnosed by clinical symptoms, an otherwise unexplained decrease in hourly urinary amylase activity >25% of baseline on 2 separate measurements, unexplained hyperamylasemia, a positive pancreas biopsy, or a combination thereof.[12] Pancreas graft loss from chronic rejection was either diagnosed by biopsy or defined as progressive deterioration of graft function over time without any other definable causes (*e.g.*, infection).

Kidney Rejection

Kidney rejection episodes were all biopsy-proven. Kidney biopsies were obtained whenever rejection was clinically suspected (based on abnormal, otherwise unexplained laboratory parameters; graft tenderness; or abnormal imaging studies).

Perioperative Care

All recipients received perioperative infection prophylaxis as follows. With the induction of anesthesia and for the first 7 days posttransplant, recipients were given imipenem–cilastatin (500 mg intravenously), either alone or with vancomycin (1000 mg intravenously). Fungal prophylaxis consisted of fluconazole (200 mg/day intravenously), given until the 14th day posttransplant. Postoperatively, nystatin swish and swallow (1×10^6 U/day) was given indefinitely. Trimethoprim–sulfamethoxazole (80/400 mg/day orally) was also given unless the recipient had a documented sulfa drug allergy. Finally, either

Table 2. SURGICAL COMPLICATIONS REQUIRING EARLY RELAPAROTOMY AFTER PANCREAS TRANSPLANTATION (BY RECIPIENT CATEGORY*)

	SPK (n = 84)		PAK (n = 35)		PTA (n = 23)	
Complications	Number of Complications	Relap (n)	Number of Complications	Relap (n)	Number of Complications	Relap (n)
Pancreas graft thrombosis	17	17	13	13	9	9
Intraabdominal infection and graft pancreatitis	36	87	10	24	8	10
Anastomotic leak	14	15	6	6	1	1
Bleeding	10	12	5	7	3	4
Other	39	22	5	7	3	3
Total	116	153	39	57	24	27

SPK = simultaneous pancreas-kidney transplant; PAK = pancreas after kidney transplant; PTA = pancreas transplant alone; Relap = early relaparotomy.
* Some recipients had more than one surgical complication at a time or more than one relaparotomy per complication.

acyclovir (for 3 months orally) or ganciclovir (for 14 days intravenously) was given to prevent cytomegalovirus infections; the doses for both drugs were adjusted according to renal function.

Early Relaparotomy

All early relaparotomies (relaps) were analyzed retrospectively. For the purpose of this study, an early relap was defined as any reoperative procedure involving the intraperitoneal or retroperitoneal space done during the first 3 months posttransplant, or during the initial pancreas transplant hospital stay if it exceeded 3 months. Perioperative care of recipients with an early relap included reduction, tapering, or complete cessation of immunosuppression as appropriate; transplant pancreatectomy and nephrectomy as necessary; and prolonged intravenous and oral antibiotic therapy as indicated.

We determined the cause for the relap (*i.e.*, the surgical complication) by reviewing preoperative, operative, and postoperative findings (*e.g.*, culture results, surgical pathology reports). Causes were classified as follows: pancreas graft thrombosis (arterial and venous, with and without concurrent kidney graft thrombosis); infection (culture-proven intraabdominal only) and pancreatitis (usually associated with infection, diagnosed at relap); anastomotic leak (duodenocystostomy or duodenal stump); bleeding (intraabdominal hemorrhage from recipient or graft tissue); and other (*e.g.*, acute cholecystitis) (Table 2). Relaps were categorized as elective or nonelective, and unrelated or related to the preceding pancreas transplant.

Perioperative mortality was defined as any death occurring within 60 days after an early relap.

Total hospital charges for the first 3 months posttransplant were determined for each recipient. Charges for hospital (re)admissions beginning before, but extending beyond, the end of the third month posttransplant were included in their entirety.

Univariate Data Analysis

Categoric variables were analyzed using the chi square test and when applicable Fisher's Exact test. Continuous variables were analyzed parametrically using Student's t test and nonparametrically using the Mann-Whitney U test.

Graft and patient survival rates were calculated according to the Kaplan-Meier procedure. The time of graft loss was determined for pancreas grafts by return to exogenous insulin use after insulin independence and for kidney grafts by return to permanent dialysis. For PAK, kidney graft survival rates refer to the date of the pancreas transplant. Calculation of patient survival included deaths occurring after kidney and pancreas graft loss. Survival rates were compared between groups using the generalized Wilcoxon test. For all univariate statistical tests, p values < 0.05 were considered significant.

Multivariate Data Analysis

Risk factors for graft and patient survival were studied respectively in four different regression analyses: all recipients, SPK only, PAK only, and PTA only. The variables studied were donor age (relative risk [RR] for each 10-year increment), preservation time (RR for each 10-hour increment), recipient age at transplantation (RR for each 10-year increment), retransplant *versus* primary

transplant, relap for graft thrombosis *versus* no relap, relap for intraabdominal infection and graft pancreatitis *versus* no relap, relap for anastomotic leak *versus* no relap, relap for bleeding *versus* no relap, and relap for other causes *versus* no relap. For all multivariate analyses, a p value < 0.15 was considered significant.

RESULTS

Early Relap

Early relap was required after 142 (32%) of 441 pancreas transplants. The relap rate (one or more relaps) was highest for SPK (36%), followed by 25% for PAK and 16% for PTA (SPK *vs.* PAK: p = 0.9; SPK *vs.* PTA: p = 0.01; PAK *vs.* PTA: p = 0.04). Multiple relaps were necessary for 9% of the transplant recipients: 12% for SPK, 9% for PAK, and 4% for PTA (SPK *vs.* PAK: p = 0.4; SPK *vs.* PTA: p = 0.1; PAK *vs.* PTA: p = 0.5). Causes of early relaps are listed in Table 2.

For 84 SPK recipients, 153 relaps were done. The most frequent cause was intraabdominal infection and graft pancreatitis (n = 36). "Other" causes (n = 39) included 1 pancreas graft arteriovenous fistula, 8 kidney graft thromboses, 2 ischemic transplant ureters, 1 pelvic lymphocele, 2 mycotic pseudoaneurysms of the iliac artery, 3 cases of metabolic acidosis and dehydration secondary to loss of pancreatic exocrine secretions, 1 reflux pancreatitis, 1 case of dysuria and urethritis secondary to exocrine pancreatic secretions, 11 cases of acute cholecystitis, 2 permanent access requirements for prolonged enteral feeding, 4 cases of colonic ischemia, 1 ileostomy (takedown), 1 fascial wound dehiscence, and 1 iliac artery perforation after insertion of an aortic balloon pump.

For 35 PAK recipients, 57 relaps were done. The most frequent cause was pancreas graft thrombosis (n = 13) (see Table 2). "Other" causes (n = 5) included one case each of ischemic transplant ureter, acute cholecystitis, fascial wound dehiscence, intraabdominal foreign body, and suspected pancreas graft ischemia.

For 23 PTA recipients, 27 relaps were done. The most frequent cause was graft thrombosis (n = 9). "Other" causes (n = 3) included 3 fascial wound dehiscences.

In all 3 recipient categories, the highest re-relap rate was for infection and graft pancreatitis (SPK, mean 2.4 re-relaps per infection; PAK, mean 2.4 re-relaps per infection; PTA, mean 1.3 re-relaps per infection).

The procedures done at the time of relap (SPK, n = 208; PAK, n = 70; PTA, n = 33) are listed in Table 3.

All relaps were nonelective and all were related to the preceding pancreas transplant. All were done as open operations, with no laparoscopic procedures.

Early Relap Timing

The time interval between the pancreas transplant and the first relap was shorter for PAK than for SPK and PTA recipients. For PAK recipients, 75% of all first relaps had taken place by day 26 *versus* day 44 for SPK and day 47 for PTA. The median was 11 days for PAK, 22 days for SPK, and 10 days for PTA (p = 0.07).

Early Conversion From Bladder to Enteric Drainage

Our study included 6 SPK recipients with early conversions from bladder to enteric drainage, done at a median of 68 days (range, 27–82 days) posttransplant. Indications for semielective early conversion were metabolic acidosis and dehydration (three), reflux pancreatitis (one), bladder leak (one), and urethritis with dysuria (one). The postoperative course after conversion was uncomplicated for all six recipients. As of December 31, 1995, with variable follow-up time (range, 187–1362 days), all these grafts are still functioning.

Transplant Pancreatectomy and Immediate Retransplant

Our study also included 8 recipients (5 SPK, 1 PAK, 2 PTA) with pancreas graft thrombosis between posttransplant day 1 and day 45. Once a suitable donor was available, all eight underwent a transplant pancreatectomy and immediate retransplant (during the same relap). Perioperative mortality for transplant pancreatectomy and immediate retransplant was 25% (2 early deaths, 1 and 45 days after the retransplant).

None of the retransplanted pancreas grafts is currently functioning. Two of the retransplanted pancreas grafts thrombosed early, 11 and 57 days after the retransplant (25% retransplant thrombosis rate). Three retransplanted pancreas grafts were lost because of rejection, 212, 264, and 309 days after the retransplant (38% graft failure rate from rejection). Two (25%) of the 8 immediately retransplanted grafts were lost because of death with a functioning graft, 45 and 749 days after the retransplant. One retransplanted pancreas graft never functioned (12% primary nonfunction rate).

Impact of Early Relap on Pancreas Graft Survival

In each of the 3 recipient categories, the rate of pancreas graft loss was significantly higher for recipients with *versus* without relap (Table 4): SPK, 74% *versus* 20%, p < 0.0001; PAK, 89% *versus* 53%, p = 0.0002; and PTA, 87% *versus* 59%, p = 0.01. Relap had a significant detrimental impact on short- and long-term pancreas graft survival in all 3 recipient categories (Figs. 1, 2, and 3). Graft

Table 3. REOPERATIVE PROCEDURES (≤3 MONTHS POSTTRANSPLANT) AFTER PANCREAS TRANSPLANTATION (BY RECIPIENT CATEGORY*)

Procedures	SPK (n = 84)	PAK (n = 35)	PTA (n = 23)
Transplant pancreatectomy	42	25	14
Transplant nephrectomy	15	1	
Pancreas retransplant (with transplant pancreatectomy)	5	1	2
Kidney retransplant (with transplant nephrectomy)	3		
Drainage of intraabdominal abscess and peripancreatic fluid, graft pancreas necrosectomy	84	26	9
Repair of leak (duodenocystostomy or duodenal stump)	13	6	1
Surgical intraabdominal hemostasis, evacuation of hematoma	13	7	4
Ligation of pancreas graft arteriovenous fistula	1		
Transplant renal vein thrombectomy	1		
Ureteroureterostomy (transplant to native ureter)	2		
Transplant ureter reimplantation		1	
Lymphocele drainage	1		
Iliac artery pseudoaneurysm repair	2		
Conversion from bladder to enteric drainage	6		
Cholecystectomy	11		
Gastrostomy tube placement	2		
Partial or subtotal colectomy, rectal stump closure, colostomy or ileostomy	4		
Ileostomy takedown	1		
Fascial wound dehiscence repair	1	1	3
Repair of iliac artery aortic balloon pump injury	1		
Foreign body removal		1	
Negative exploratory laparotomy		1	
Total procedures	208	70	33

SPK = simultaneous pancreas-kidney transplant; PAK = pancreas after kidney transplant; PTA = pancreas transplant alone; Relap = early relaparotomy.
* Some recipients had more than one reoperative procedure done at once, or over time.

survival rates at 1 and 5 years, respectively, for recipients with *versus* without relap were SPK, 32% and 20% *versus* 82% and 70%, p = 0.0001 (see Fig. 1); PAK, 11% and 11% *versus* 71% and 38%, p = 0.0001 (see Fig. 2); and PTA, 26% and 8% *versus* 60% and 35%, p = 0.0001 (see Fig. 3).

The overall Cox regression analysis for pancreas graft survival showed that even after adjusting for early relaps, both PAK (RR = 1.8, p = 0.0004) and PTA (RR = 1.8, p = 0.0004) recipients were at significantly higher risk for graft loss than were SPK recipients.

In the categorywise Cox regression analyses (Table 5), significant risk factors for graft loss were: 1) SPK recipients: older donor age (RR = 1.1), relap for pancreas graft thrombosis (RR = 22), and relap for intraabdominal infection and graft pancreatitis (RR = 3.6); 2) PAK recipients: older donor age (RR = 1.2), retransplant status (RR = 1.5), relap for pancreas graft thrombosis (RR = 15.0), relap for intraabdominal infection and graft pancreatitis (RR = 9.3), relap for anastomotic leak (RR = 5.6), relap for bleeding (RR = 3.6), and relap for other causes (RR = 3.8); and 3) PTA recipients: relap for pancreas graft thrombosis (RR = 9.4).

Impact of Early Relap on Kidney Graft Survival

For SPK recipients, the overall rate of kidney graft loss was significantly higher for those with *versus* without early relap (40% *vs.* 26%, p = 0.02; see Table 4). Accordingly, kidney graft survival rates at 1 and 5 years, respectively, were lower for SPK recipients with *versus* without relap (59% and 53% *vs.* 83% and 69%, p = 0.0001; Fig. 4).

For PAK recipients, the rate of kidney graft loss due to death with a functioning graft was significantly higher for those with *versus* without early relap (20% *vs.* 6%, p = 0.04; see Table 4). Kidney graft survival rates at 1 and 5 years, respectively, for PAK recipients with *versus* without relap were 82% and 78% *versus* 97% and 78% (p = 0.06; Fig. 5).

Impact of Relap on Patient Survival

Perioperative mortality for early relap was 11% (n = 9) for SPK, 9% (n = 3) for PAK, and 4% (n = 1) for PTA recipients. Overall, the mortality for early relap was significantly higher for retransplant recipients than for primary transplant recipients: 21% (n = 6) *versus* 6% (n = 7), p = 0.03.

Table 4. CAUSE OF PANCREAS AND KIDNEY GRAFT LOSS (BY RECIPIENT CATEGORY AND RELAPAROTOMY STATUS)

	SPK (n = 236)		PAK (n = 101)		PTA (n = 104)	
	Relap (n = 84)	No Relap (n = 152)	Relap (n = 35)	No Relap (n = 66)	Relap (n = 23)	No Relap (n = 81)
Cause of pancreas graft loss						
Graft thrombosis	18	2	10	0	9	0
Infection and pancreatitis	24	0	7	1	1	1
Anastomotic leak	0	0	2	1	0	0
Bleeding	4	0	2	0	1	0
Acute rejection	2	4	3	5	2	7
Chronic rejection	8	14	5	23	6	38
Death with a functioning graft	6	20	2	5	1	2
Total pancreas graft losses	62 (74%)*	40 (26%)*	31 (89%)†	35 (53%)†	20 (87%)‡	48 (59%)‡
Cause of kidney graft loss						
Graft thrombosis	12	2	0	0	—	—
Acute rejection	7	5	0	0	—	—
Chronic rejection	6	14	0	6	—	—
Death with a functioning graft	9	19	7‖	4‖	—	—
Total kidney graft losses	34§ (40%)	40§ (26%)	7 (20%)	10 (15%)	—	—

SPK = simultaneous pancreas-kidney transplant; PAK = pancreas after kidney transplant; PTA = pancreas transplant alone; Relap = early relaparotomy.
* $p < 0.0001$ for SPK-Relap *vs.* SPK-No Relap.
† $p = 0.0002$ for PAK-Relap *vs.* PAK-No Relap.
‡ $p = 0.01$ for PTA-Relap *vs.* PTA-No Relap.
§ $p = 0.02$ for SPK-Relap *vs.* SPK-No Relap.
‖ $p = 0.04$ for PAK-Relap *vs.* PAK-No Relap.

By univariate analysis, we noted 51 (22%) deaths for SPK recipients (no relap [29], 19%; relap [22], 26%, p = 0.2). For PAK recipients, we noted 18 (18%) deaths (no relap [10], 15%; relap [8], 23%, p = 0.33). For PTA recipients, we noted 12 (12%) deaths (no relap [7], 9%; relap [5], 22%, p = 0.1).

Short- and long-term patient survival rates were lower in all recipient categories for those with *versus* without relap. Patient survival rates at 1 and 5 years, respectively, for recipients with *versus* without relap were SPK, 77% and 65% *versus* 87% and 78% (p = 0.04; Fig. 6); PAK, 79% and 76% *versus* 98% and 81% (p = 0.02; Fig. 7); and PTA, 80% and 74% *versus* 95% and 90% (p = 0.03; Fig. 8).

Multivariate Analysis of Impact of Relap on Patient Survival

The overall Cox regression analysis showed that the risk of death was significantly higher for SPK *versus* PAK

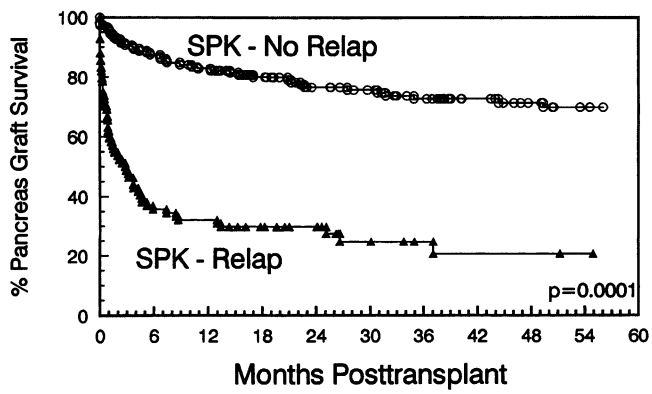

Figure 1. Pancreas graft survival rates for simultaneous pancreas-kidney (SPK) transplant recipients with *versus* without early relaparotomy.

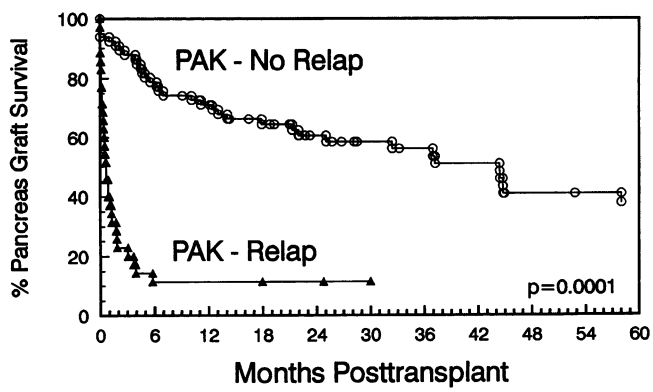

Figure 2. Pancreas graft survival rates for pancreas after kidney (PAK) transplant recipients with *versus* without early relaparotomy.

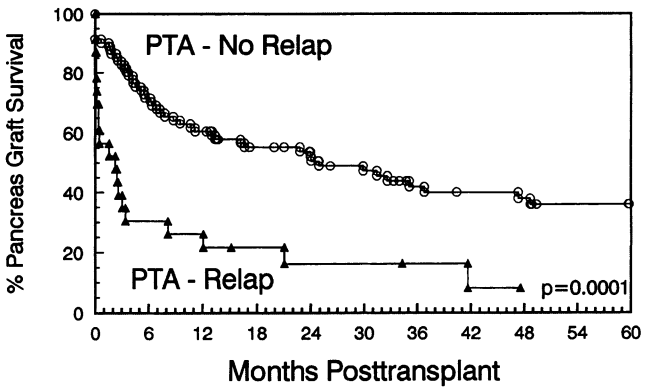

Figure 3. Pancreas graft survival rates for pancreas transplant alone (PTA) recipients with *versus* without early relaparotomy.

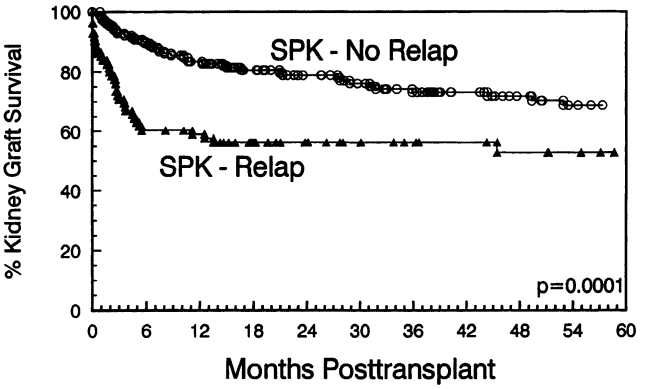

Figure 4. Kidney graft survival rates for simultaneous pancreas-kidney (SPK) transplant recipients with *versus* without early relaparotomy.

recipients (RR = 1.6, p = 0.1) and for SPK *versus* PTA recipients (RR = 1.9, p = 0.07).

In the categorywise Cox regression analyses (Table 6), significant risk factors for death were: 1) SPK recipients: older recipient age (RR = 1.4), retransplant status (RR = 2.3), relap for infection and graft pancreatitis (RR = 2.2), and relap for anastomotic leak (RR = 2.3); 2) PAK recipients: older recipient age (RR = 2.6), retransplant status (RR = 6.2), and relap for thrombosis (RR = 7.6); and 3) PTA recipients: longer preservation time (RR = 3.6) and relap for bleeding (RR = 21.7) (see Table 6).

Economic Impact of Early Relap

Median total hospital charges for the first 3 months posttransplant were significantly higher in all 3 recipient categories for those with *versus* without relap: SPK, $169,000 (range, $30,000–$765,700) *versus* $101,700 (range, $51,900–$369,000), p = 0.0001; PAK, $108,500 (range, $21,500–$195,600) *versus* $73,000 (range, $22,800–$194,900), p = 0.0001; PTA, $126,900 (range, $71,200–$196,700) *versus* $78,200 (range, $20,300–$285,500), p = 0.0001.

DISCUSSION

Pancreas transplants, compared with the other routinely performed solid organ transplants, still have the highest rate of technical failures, serious intraabdominal complications, and reoperations.[2,13–20] In contrast to most other transplant recipients and most nonimmunocompromised patients undergoing major general surgical procedures, pancreas recipients have a number of strikes against them: they are exclusively diabetic, often with already-estab-

Table 5. COX REGRESSION ANALYSIS* FOR GRAFT LOSS (BY RECIPIENT CATEGORY)

	SPK (n = 236)		PAK (n = 101)		PTA (n = 104)	
	RR	p	RR	p	RR	p
Donor age (per 10-yr increment)	1.1	0.13	1.2	0.13		
Preservation time (per 10-hr increment)						
Age at transplantation (per 10-yr increment)						
Retransplant *vs.* primary transplant			1.5	0.13		
Relaparotomy for pancreas graft thrombosis	22	0.0001	15.0	0.0001	9.4	0.02
Relaparotomy for intraabdominal infection and graft pancreatitis	3.6	0.0001	9.3	0.004		
Relaparotomy for anastomotic leak			5.6	0.007		
Relaparotomy for bleeding			3.6	0.06		
Relaparotomy for other causes			3.8	0.03		

SPK = simultaneous pancreas-kidney transplant; PAK = pancreas after kidney transplant; PTA = pancreas transplant alone; RR = relative risk.
* Relative risk and p value given only if $p < 0.15$.

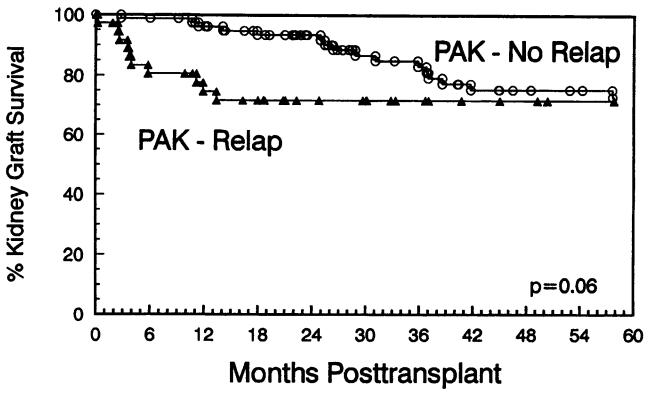

Figure 5. Kidney graft survival rates for pancreas after kidney (PAK) transplant recipients with *versus* without early relaparotomy.

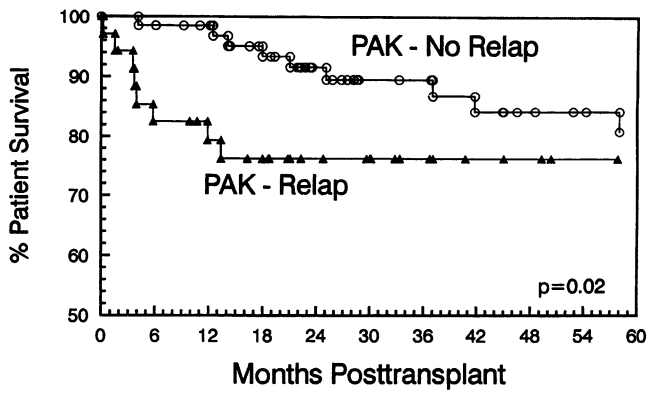

Figure 7. Patient survival rates for pancreas after kidney (PAK) transplant recipients with *versus* without early relaparotomy.

lished manifestations of secondary diabetic end-organ damage; they receive more frequent and longer anti-T-cell induction therapy; and they undergo an operation that involves two hollow viscera (duodenum and bladder). SPK recipients are uremic or preuremic at the time of their long, technically demanding dual-organ transplant. PAK recipients are already chronically immunosuppressed at the time of their pancreas transplant. Also, in the early postoperative period, pancreas recipients develop earlier and more severe rejection episodes (requiring additional courses of anti-T-cell therapy) than kidney-alone recipients.[21]

It is surprising that these surgical complications after pancreas transplantation have received little attention to date. Moreover, the few published reports on this subject fail to provide a segregated analysis for those with *versus* without complications, with respect to morbidity as well as graft and patient survival.[14,15,17] Hence, it is difficult to evaluate the absolute and relative impact of major surgical complications on long-term outcome. It is difficult, too, to develop strategies to diminish the negative consequences of these complications, not only for individual recipients but also for the sake of the growing acceptance and popularity of pancreas transplantation.[2]

This lack of data and knowledge stimulated us to study all intraabdominal surgical complications requiring relap in 441 consecutive, whole organ, bladder-drained pancreas transplants done at our institution over an 8-year period. Given the increasing need for accountability from an economic perspective, especially in light of the ongoing reorganization of the health-care sector, we also assessed the additional cost caused by these adverse events.

Our overall relap rate was 32%. This result appears high compared with the relap rates after general surgical operations (usual range 2%–5%).[22–24] However, it is in line with reported rates from other pancreas transplant centers. The Milan group reported a 20% relap rate after 10 bladder-drained pancreas transplants.[16] The Wisconsin group reported a 31% rate of surgical complications (apparently mostly treated by relap).[14] The Nebraska group noted a 36% relap rate for their pancreas recipients.[17] In a study representative of the early experience with enteric-

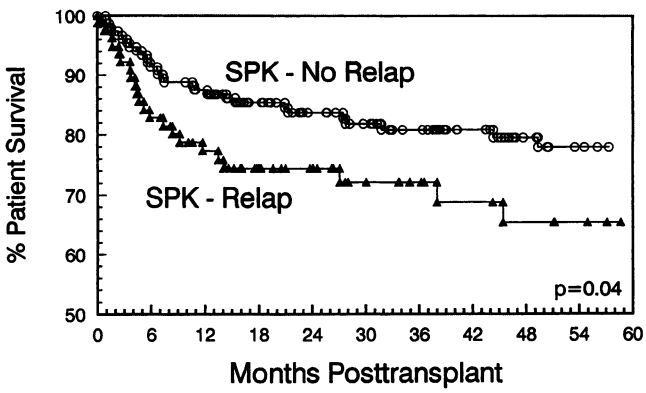

Figure 6. Patient survival rates for simultaneous pancreas-kidney (SPK) transplant recipients with *versus* without early relaparotomy.

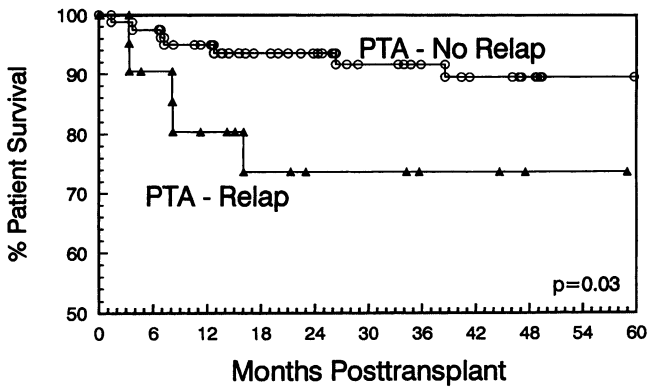

Figure 8. Patient survival rates for pancreas transplant alone (PTA) recipients with *versus* without early relaparotomy.

Table 6. COX REGRESSION ANALYSIS* FOR RECIPIENT DEATH (BY RECIPIENT CATEGORY)

	SPK (n = 236)		PAK (n = 101)		PTA (n = 104)	
	RR	p	RR	p	RR	p
Donor age (per 10-yr increment)						
Preservation time (per 10-hr increment)					3.6	0.01
Age at transplantation (per 10-yr increment)	1.4	0.05	2.6	0.01		
Retransplant *vs.* primary transplant	2.3	0.05	6.2	0.001		
Relaparotomy for pancreas graft thrombosis			7.6	0.007		
Relaparotomy for intraabdominal infection and graft pancreatitis	2.2	0.03				
Relaparotomy for anastomotic leak	2.3	0.09				
Relaparotomy for bleeding					21.7	0.002
Relaparotomy for other causes						

SPK = simultaneous pancreas-kidney transplant; PAK = pancreas after kidney transplant; PTA = pancreas transplant alone; RR = relative risk.
* Relative risk and p value given only if $p < 0.15$.

drained pancreas grafts, the Stockholm group reported a 65% relap rate after 43 pancreas transplants.[18]

In our study, multiple relaps were required for 28% of all recipients with surgical complications. This number is higher than the multiple relap frequency for general surgical patients with intraabdominal surgical complications: Hinsdale et al.[24] reported a multiple relap rate of 8% for nonimmunosuppressed patients with intraabdominal sepsis, and Kirk[23] noted a 16% multiple relap rate for patients with early complications after abdominothoracic operations. Our high multiple relap rate for pancreas recipients underscores another finding of our study: none of the operative reinterventions could be done laparoscopically because the complications were too severe. In this regard, it is important to mention that we routinely perform laparoscopic general surgery procedures, as well as laparoscopic procedures for post-kidney transplant complications.[25] Our pancreas findings stand in stark contrast to our experience with other solid organ grafts, such as kidneys, where the relap rate, according to a previous study,[20] was only 6%.

By recipient category, our pancreas transplant relap rate (overall and multiple) was significantly higher for SPK and PAK recipients than for PTA recipients. This finding may reflect the technically more involved and demanding dual-organ transplant procedure for SPK uremic or preuremic recipients or the longstanding chronically immunosuppressed state of PAK recipients. Complications in our PAK recipients were diagnosed earlier than in SPK and PTA recipients, which may also be due to their chronically immunosuppressed—and thus more complication-prone—state at the time of their pancreas transplant. In a previous study, we showed that pancreas graft thrombosis, the most frequent cause of relap in PAK recipients in our current study, was significantly more common in PAK recipients, possibly because of the procoagulant effects of their longstanding immunosuppression with CsA and steroids.[6] Their chronic pretransplant immunosuppression could also explain why intraabdominal infections, the second most common cause of relap in PAK recipients, would become symptomatic earlier in PAK recipients.

The overall most frequent causes of relap were infection, thrombosis, and anastomotic leak. These findings are consistent with previously published reports by Ozaki et al.,[17] Eckhoff et al.,[14] and Douzdjian et al.[15] However, it is surprising that anastomotic leak, pertaining mostly to the surgical technique, remains so prominent almost one decade after publication of the standardized and widely accepted bladder drainage technique.[11,26] Current results are better than those of historical controls (which were mostly enteric-drained[18]), yet clearly there is still room for improvement in surgical technique. The bladder drainage technique must be further refined.

Pancreas graft survival rates after early reoperation were significantly lower in all three recipient categories. This high pancreas graft loss rate was also reflected in a transplant pancreatectomy rate within the first 3 months of 50% for SPK, 71% for PAK, and 61% for PTA. The most significant graft survival risk factors were relap for thrombosis (which almost universally results by itself in graft failure, with salvage rare) (SPK, PTA) and relap for infection (SPK). But for PAK recipients, relap for any cause was associated with a higher risk for graft loss,

consistent with the previously discussed considerations specific to this category.

The literature also lacks data on the implications of pancreas graft-related complications on a previously or simultaneously placed kidney graft. In our study, the kidney graft survival rates were significantly lower after an early relap. For SPK recipients, these increased kidney graft losses were mainly due to kidney graft thrombosis and acute rejection, compared with those not undergoing relap. The SPK kidney graft thrombosis rate may be explained by the presence of the same donor (*e.g.*, age) and recipient (*e.g.*, hypercoagulability) risk factors that affect not only the pancreas but also the kidney graft.[6] The increased incidence of kidney graft loss from acute rejection may be due to the reduced, tapered, or discontinued immunosuppression that is often necessary in cases of severe, life-threatening intraabdominal infections and cases of pancreatitis.

For PAK recipients, kidney graft survival rates were also worse after a pancreas-related relap. These kidney graft losses are particularly disconcerting and merit further attention because they occurred in engrafted, established, and well-functioning organs that frequently originated from living related donors. This heavy loss of functioning kidney grafts was not due to immediate, local intraabdominal implications of pancreas-related complications, but rather due to an increased rate of death with a functioning graft (*e.g.*, cardiovascular deaths in septic-hypermetabolic, critically ill PAK recipients). Given the steadily growing kidney waiting list, all possible efforts must be directed at minimizing the loss of precious kidney grafts and thus increasing the acceptance and success rates of the PAK procedure itself.

The overall perioperative relap mortality rate in our immunocompromised recipient population was 9%. This result compares favorably with the relap mortality rate observed after general surgical abdominal operations. After abdominal and abdominothoracic operations, Hinsdale et al.[24] reported a relap mortality rate of 43%, Zer et al., 38%,[22] Lorenc, 40%,[27] and Kirk, 43%.[23] For pancreas transplants, only Ozaki et al.[17] have published data that allows a direct comparison: the perioperative relap mortality rate was 0% for their 61 SPK recipients and 16% for their 12 solitary pancreas recipients. The outcome in Ozaki's and our study is far better than the published general surgical perireoperative mortality rates for reoperations. Reasons may include increased vigilance in heavily immunocompromised recipients, leading to earlier diagnosis and treatment; greater experience in routinely managing those complications, because they are so frequent; and prescreening of our recipient population.[8]

In light of the magnitude of the interventions (see Table 4), it is not surprising that early relap significantly decreased our patient survival rates in all 3 recipient categories. Interestingly, the category-specific profiles of highest-risk complications differed considerably: for SPK, infection and pancreatitis as well as leaks; for PAK, thrombosis; and for PTA, bleeding.

Given the extent of the reoperations and the frequency of multiple relaps, median hospital charges increased by $67,300 (SPK), $35,500 (PAK), and $48,700 (PTA) for those with at least one early relap *versus* those without. Thus, the median cost of pancreas transplants with (*vs.* without) surgical complications was augmented by 66% (SPK), 49% (PAK), and 62% (PTA). Kalish et al.[28] studied costs of complications for 372,680 major surgery patients admitted to California acute care hospitals in 1988 and noted that, on average, patients with (*vs.* without) complications incurred total hospital charges $16,023 (96.6%) higher. Although their study had several important limitations, they concluded that preventing or minimizing even a portion of such complications could yield substantial overall savings to the health-care system. Coello et al.[29] studied the cost of infection in 67 surgical patients in a United Kingdom hospital and noted a significant mean extra cost for those with an infection. In their study, length of hospital stay was the greatest contributor, accounting for 92% of the extra costs in general surgery. The results of our economic impact analysis are, therefore, in line with these two studies in nonimmunocompromised patients, especially because the relaps in our population led almost invariably to an extended hospital stay and were frequently caused by an infection.

Optimization and rationalization of posttransplant care (*e.g.*, minimizing expenses for immunosuppressants by drug level monitoring, avoiding unnecessary laboratory tests) are important strategies. But any improvement in the surgical complication rate may have an even bigger impact on the overall cost of pancreas transplantation, especially because substantially higher hospital charges were incurred by almost one third of all pancreas recipients. Quantifying the cost of surgical complications after pancreas transplantation, as our study does, may increase the willingness of health insurance providers to cover the cost, say, of prolonged antimicrobial prophylaxis—provided that such prophylaxis is shown to be effective.

Another important finding of our study is the wide surgical spectrum of the procedures done at relap. Extremely diverse areas (hepatobiliary, gastric, small and large intestinal, native vascular, and urinary tract systems, plus the transplanted organs themselves) were involved. Ideally, certified pancreas transplant surgeons should be able to manage all of these complications themselves rather than rely on a multitude of expensive surgical consultants. In an era of diagnosis-related groups (DRGs) and capitation, this wide reoperative surgical spectrum must be taken into account when establishing certification criteria in pancreas transplantation, particularly if they are

also to apply to graduates whose primary specialty is not general surgery.

Our study also provides an interesting follow-up to our experience with conversion from bladder to enteric drainage. Previously, early posttransplant conversion was not advocated, in order to allow maximal tapering of the immunosuppression and optimal immunologic monitoring of the pancreas graft (using the urinary amylase level) during the particularly critical engraftment period; only then did the conversion operation proceed.[30] Accordingly, in a previous report by Gruessner et al.,[30] the median time from transplantation to conversion was 11 months. With increasing experience with the conversion procedure, we have now done 6 early (≤3 months posttransplant) conversions in SPK recipients, as reported herein, without any technical or immunologic pancreas graft failure. These encouraging preliminary results for SPK recipients—where we can still use the kidney for immunologic monitoring of the pancreas after conversion—await larger numbers and longer follow-up.

Previous reports suggested that transplant pancreatectomy and immediate retransplantation might be an option for a subset of recipients with very early graft failure (thrombosis). Fernandez-Cruz et al.[31] described one case of pancreas graft thrombosis with immediate successful retransplantation. Boudreaux et al.[32] described a multicenter experience: eight immediate regrafts after transplant pancreatectomy at four institutions had encouraging initial results in all but one patient. However, in our current single-center report with more patients and longer follow-up, we noted a dismal perioperative mortality rate for transplant pancreatectomy and immediate retransplantation (25%), as well as poor overall graft survival. In light of these results, we believe this strategy should no longer be considered for patients with early pancreas graft failure.

Given the deleterious consequences of early surgical complications, we believe that a major effort must be directed at preventing them to begin with. In our study the outcome was poor, despite our liberal policy of early and timely reexploration, our high pancreas graft removal rate, and our modern critical care facilities at a tertiary academic health-care center. Thus, from a clinical perspective, the implications of our findings are as follows.

First, regarding recipient selection criteria, our current aggressive coronary and cardiovascular pretransplant screening may suffice to predict a good outcome for those *not* having a surgical complication and *not* requiring a relap. But for a significant subset of prospective recipients in our study, this approach was clearly insufficient and not predictive of the mortality when severe physiologic stress and hypermetabolism caused by reoperations and sepsis occurred. With our increasing understanding of the molecular mechanisms of the systemic hypermetabolic postinjury response, it may become possible to predict who will (*vs.* will not) tolerate complications (particularly with regard to patient survival). But for now, older recipients should not be considered for any type of pancreas transplant, given their higher risk for death (particularly SPK and PAK). The increase in risk associated with the increase in age is continuous and not limited to a specific threshold age limit. For clinical purposes, transplantation needs to be strongly reconsidered for type I insulin-dependent diabetics over age 45. Moreover, retransplantation should be avoided as a routine measure (SPK, PAK); it should be considered only, if at all, for highly selected recipients on a case-by-case basis. In our study, retransplantation was associated with an increased risk of graft loss (PAK) as well as of death (SPK, PAK).

Second, regarding donor selection and organ procurement, older donors should generally be excluded. As for recipient age, the risk of premature graft loss (SPK, PAK) increased continuously with increasing donor age, without being limited to a specific donor age threshold. For clinical purposes, donors over age 45 should be seriously reconsidered. Moreover, preservation time needs to be minimized. In our multivariate analysis, longer preservation times were directly associated with an increased risk of death (PTA), and indirectly with an increased likelihood of postreperfusion pancreatitis (which in turn increases graft loss and patient death rates by more frequently mandating relap).

Accepting older donors or longer preservation times to improve HLA matching is ill advised. The trade-off is a higher graft loss rate and, more importantly, a higher mortality rate. Accepting the well-described risk of the higher thrombosis rate with older donor grafts is also ill advised.[6] The penalty for an early relap due to thrombosis is deadly: an increased mortality rate, especially for PAK recipients (*i.e.*, those with the highest thrombosis risk).

Third, regarding the operative aspects of the transplant procedure itself, a meticulous surgical technique cannot be overemphasized. Thrombosis rates must be minimized by selecting and using the appropriate arterial revascularization benchwork technique, and by placing the pancreas graft in the anatomically optimal position in the recipient (as discussed in a previous report).[6] The closure of the proximal and distal duodenal stump and the duodenovesical anastomosis itself must be done without making any compromises or sacrifices for the sake of a shorter operating time or a technical shortcut. An accurate and meticulous surgical technique with minimal mechanical manipulation of the pancreas graft will also decrease the likelihood of infection and pancreatitis as well as avoid bleeding, all of which were risk factors in our study for decreased graft and patient survival after relap.

Because of the retrospective nature of our study, we could not draw any inferences with regard to the value of

antimicrobial prophylaxis. Future prospective randomized trials must assess protocols involving sterilization of the donor duodenal segment; the absolute and relative value of administering various antimicrobial (antibacterial and antifungal) agents, including optimal peritransplant duration; and intraoperative antimicrobial prophylaxis (*e.g.*, abdominal irrigation with antibiotic solutions in the recipient).

Future studies must also further analyze the impact of agents with a potentially favorable influence on pancreas preservation injury. Unfortunately, little progress has been achieved in this area. Octreotide, a synthetic somatostatin analog, inhibits exocrine pancreatic secretion[33] and may even downregulate activated immune cells.[34] But in one small randomized study, the incidence of posttransplant infection, pancreatitis, and reoperation was not significantly different between the control and the octreotide group.[35] Moreover, the outcome of large animal experiments suggests that octreotide inhibits insulin release[33] and decreases blood flow to the transplanted pancreas.[36] Preliminary results of a retrospective study of 41 pancreas transplant patients by Grewal et al.[37] suggest that donor pretreatment with high-dose steroids, as well as postoperative administration of calcium channel blockers to the recipient, may prevent acute pancreatitis.[37] But these findings await confirmation in a larger, randomized, prospective trial.

Fourth, our results provide clear guidelines regarding care of pancreas recipients who develop any early complications. Irrespective of the recipient category, removing the pancreas graft should be considered as soon as a graft-related surgical complication is diagnosed and relap is required. Transplant pancreatectomy should be routine not only for early thrombosis, but frequently also for infection and pancreatitis. For recipients with a leak or bleeding, surgical correction should be considered if: 1) the site can be readily identified at the first reexploration; 2) it can be easily and safely repaired; and 3) there is no other concomitant risk factor, such as gross intraabdominal infection. Every time surgical correction of leaks and bleeding is attempted, the risks associated with the repair and the potential need for a re-relap must be weighed against the increased risk of graft loss and death, particularly for SPK and PAK recipients. From our analysis, for all pancreas graft-related complications requiring relap, the focus must switch immediately from the preservation of graft function to the preservation of the recipient's life. In contrast, other intraabdominal interventions (*e.g.*, cholecystectomy for acute cholecystitis) can be done safely, without increased risk of graft loss and patient death, even during the early posttransplant period.

Finally, even after adjusting for surgical complications, the solitary pancreas recipients (PAK and PTA) in our study had a higher risk of graft loss. Although technical failures have been touted as a major impediment to the further popularization of solitary pancreas transplantation,[2] a two-pronged approach will instead be necessary: first, surgical complications and their sequelae must be minimized, as discussed here, and second, but equally important, efforts must be made toward more efficient host immunomodulation. Improved immunosuppression would not only decrease immunologic graft failures, but also improve, if not the incidence, then at least the outcome of surgical complications. For example, the incidence of infections may or may not decrease, but they would become easier to manage and have a lower mortality rate. Accordingly, future studies must investigate whether recently introduced immunosuppressants (e.g., tacrolimus and mycophenolate mofetil)[38] also entail a lower incidence of, and better prognosis for, early surgical complications. All these measures would enhance the role of pancreas transplantation for type I insulin-dependent diabetics who are still very early in the course of their inexorable progression toward severe secondary diabetic complications and end-organ damage.

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