The Surgical Risk of Pancreas Transplantation in the Cyclosporine Era: An Overview

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Background: Pancreas transplants are still associated with the highest surgical complication rate of all routinely performed solid organ transplants. To date, the impact of serious surgical complications in the cyclosporine era on perioperative patient morbidity, graft and patient survival, and hospital costs has not been analyzed in detail.

Study Design: We retrospectively studied surgical complications after 445 consecutive pancreas transplants (45% simultaneous pancreas-kidney [SPK], 24% pancreas after kidney [PAK], and 31% pancreas transplant alone [PTA]). Of these, 80% were primary transplants, 20% were retransplants. Cadaver donors were used in 92%, living related donors in 8%. To develop guidelines for their prevention and management, we studied the impact of significant surgical complications (intra-abdominal infections, vascular graft thrombosis, and anastomotic leak) requiring relaparotomy on graft and patient survival.

Results: Relaparotomy was required after 32% of all pancreas transplants (SPK: 36%, PAK: 25%, PTA: 16% [p = 0.04]). Perioperative mortality was 9%. Graft and patient survival rates were significantly lower for recipients with (versus without) relaparotomy. The most common procedures were drainage of intra-abdominal abscess with graft necrosectomy (50% of all relaparotomies) and transplant pancreatectomy (34%). The most common causes of relaparotomy were intra-abdominal infection, vascular graft thrombosis, and anastomotic leak. Intra-abdominal infection occurred in 20% (SPK: 18%, PAK: 24%, PTA: 20% [p = NS]). The rate was significantly higher for living related donor (42%) versus cadaver donor (18%) recipients and for those with enteric-drained (39%) versus bladder-drained (18%) transplants. Graft and patient survival rates were significantly lower for recipients with (versus without) intra-abdominal infection. Outcome was better after bacterial (versus fungal) infections. For SPK recipients, those not on dialysis before transplant had significantly higher graft survival than those on dialysis. Vascular graft thrombosis occurred in 12% of all recipients. The rate was significantly higher for PAK (21%) than for PTA (10%) and SPK (9%) recipients. It was significantly lower for recipients of grafts with donor iliac Y-graft reconstruction (versus all other types of arterial reconstruction) and with right-sided (versus left-sided) graft placement. Of note, patient survival was not different for recipients with versus without vascular graft thrombosis. The incidence of anastomotic or duodenal stump leaks was 10%; of these recipients, 70% required relaparotomy. Patient and graft survival rates were no different for recipients with versus without leaks.

Conclusions: Serious surgical complications occurred in 35% of pancreas recipients and had a significant impact on patient and graft survival. Based on multivariate risk factor analyses, we recommend the following: donors over 45 years and those dying of cerebrocardiovascular disease should not be used; recipients over 45 years and those with a history of cardiac disease should be considered for a kidney transplant alone (KTA); surgical technique for graft procurement, preparation, and implantation should be meticulous; right-sided implantation and arterial Y-graft reconstruction should be performed when possible, since they had the highest success rates; when complications require relaparotomy, the focus must switch from graft salvage to life preservation; and the threshold for pancreatectomy should be low. Diagnosis should be timely, and treatment and relaparotomy expedited. These cornerstones of success should help decrease the risk of surgical complications and mortality after pancreas transplants. (J Am Coll Surg 1997;185:128–144. © 1997 by the American College of Surgeons)
Pancreas transplantation is currently the only treatment of type I diabetes mellitus that routinely and consistently restores continuous normoglycemia and normalizes longterm hemoglobin A1C levels. Pancreas transplantation has gained significant popularity over the past decade. In 1995, for the first time, over 1,000 pancreas transplants were reported—from the United States alone—to the International Pancreas Transplant Registry, which has data on a total of 8,500 pancreas transplants worldwide between June 1976 and July 1996 (1). Overall 1-year patient survival rates now exceed 90%; pancreas graft survival rates are 70% (2). The increasingly widespread application of pancreas transplantation is a result of improved outcomes secondary to technical refinements of the transplant procedure itself (eg, bladder drainage technique); more potent immunosuppressive regimens (eg, quadruple therapy for induction, new immunosuppressants such as tacrolimus and mycophenolate mofetil); more accurate diagnosis of rejection (eg, percutaneous, transcystoscopic, and laparoscopic biopsies); more efficient yet less toxic antiviral (eg, ganciclovir), antifungal (eg, fluconazole), and antibacterial (eg, triazoles) agents for prophylaxis and treatment of posttransplant infection, and better selection of donors and recipients (eg, limiting the number of donors and recipients > 45 years of age) (3–9).

Pancreas transplantation was originally conceived as a definitive surgical therapy for a metabolic disease, but it remains a challenge to surgeons because of the diversity and complexity of surgical complications. According to a recent International Pancreas Transplant Registry report, between 11% and 21% of all pancreas grafts are lost because of surgical complications such as intra-abdominal infection, vascular graft thrombosis, and anastomotic leak (1, 2). Minimizing surgical complications would not only decrease morbidity and mortality rates, but also provide additional impetus for even more widespread application, especially because pancreas transplantation is not considered life saving.

In our series of 445 consecutive pancreas transplants between January 1, 1986 and July 31, 1994 (cyclosporine era), we reviewed the most serious surgical complications, (ie, all those requiring reoperation). The purpose of this retrospective review was twofold: first, to assess the perioperative morbidity and implications for longterm graft and patient survival of surgical complications, and second, to study the spectrum of the complications that pancreas transplant surgeons have to manage. We also analyzed in detail the three most common causes for surgical reexploration: intra-abdominal infection, vascular graft thrombosis, and anastomotic leak. Because of the multitude of donor and recipient risk factors that potentially affect pancreas transplant outcome, we applied multivariate analysis to all three recipient categories: simultaneous pancreas–kidney transplant (SPK), pancreas after kidney transplant (PAK), and pancreas transplant alone (PTA). Special consideration was given to the technical aspects of the transplant procedure itself, their implications for infectious and vascular complications, and the treatment of posttransplant surgical complications.

Methods

Study population. We reviewed the most serious surgical complications (ie, all those requiring reoperation) after 445 consecutive pancreas transplants done at our institution between January 1, 1986 and July 31, 1994. Cadaver donors were used in 409 (92%) transplants, and living related donors in 36 (8%) transplants. There were 357 (80%) primary transplants and 88 (20%) retransplants. Of the latter, 68 were first, 17 second, and 3 third retransplants.

Of these 445 pancreas transplants, 199 (45%) were SPK, 138 (31%) were PTA, and 108 (24%) were PAK. Of the 380 recipients, 375 were white, 3 were Native American, and 2 were black. The average recipient age was 33 ± 6 years (range, 19–59 years). For management of pancreas exocrine secrections, bladder drainage was used in 399 (90%) transplants, enteric drainage in 43 (10%), and duct injection in 3 (1%). For cadaver donor transplants, bladder drainage was most common (389 of 409; 92%); for living related donor transplants enteric drainage was most common (21 of 36; 58%). Donor and recipient selection criteria have previously been detailed (9).

Surgical technique

Donor operation (10). Combined pancreas–liver–kidney specimens were procured as follows. At laparotomy, the presence of an aberrant or accessory right or left hepatic artery is ruled out by inspection and palpation of the hepatoduodenal and gastrohepatic ligaments. After a Kocher maneuver, the hepatoduodenal ligament is dissected along the superior border of the pancreas to iden-
tify the common bile duct, common hepatic artery, and portal vein. The common bile duct and the gastroduodenal artery are identified, ligated, and divided. The common hepatic artery is mobilized in a retrograde fashion toward the celiac axis; the splenic artery takeoff is identified and dissected circumferentially. The takeoff of the celiac axis from the aorta is identified, and the suprarena- liac aorta is looped.

The splenocolic ligament and the retroperitoneal attachments of the spleen are divided. With the spleen as a handle to minimize mechanical trauma, the pancreas is then dissected off its retroperitoneal attachments. During mobilization of the lower pancreatic margin, the inferior mesenteric vein is ligated and divided. The pancreatic dissection and mobilization are continued to the left lateral aspect of the abdominal aorta.

A nasogastric tube is advanced across the pylorus into the duodenum, which is flushed with 250 mL of normal saline solution containing cefazolin sodium (4,000 mg/L), amikacin (2,000 mg/L), and amphotericin B (200 mg/L). The nasogastric tube is pulled back into the stomach. The duodenum is stapled and transected proximally and distally at the ligament of Treitz using a GIA (gastrointestinal anastomosis) stapler.

The donor is systemically heparinized, and the suprarenal abdominal aorta is cross-clamped. The liver, pancreas, and kidneys are flushed in situ with University of Wisconsin preservation solution via the lower abdominal aorta. The intra-abdominal organs are cooled with topical ice slush. Systemic venous venting is done through the right atrium or the infrarenal vena cava. At the same time, a portal flushing cannula is inserted into the portal vein, and the portal vein is transected close to the porta hepatis to decompress pancreatic outflow. The pancreas is then removed, leaving the celiac axis and the SMA identified. After the aortic flush is begun, the portal vein is transected distally at the porta hepatis to decompress pancreatic outflow. The pancreas is then removed, leaving the celiac axis and the SMA takeoffs on a common aortic Carrel patch. All other steps are then done as previously described.

Pancreas graft preparation (10, 11). The back table preparation is always done with the pancreas immersed in University of Wisconsin preservation solution at 4°C. After removal of the spleen, the vascular bundles of the transverse colonic and small bowel mesentery are re-ligated and shortened. The proximal duodenal staple line is oversewn and inverted using Prolene sutures.

Three techniques are used for arterial reconstruction after combined pancreas-liver procurement:

1. Y-graft reconstruction (most frequent), using the donor iliac artery bifurcation (after shortening the SMA, an end-to-end anastomosis to the donor external iliac artery is created; the donor iliac artery is anastomosed end-to-end to the splenic artery, leaving the proximal common donor iliac artery for anastomosis to the recipient inflow vessel)

2. End-to-side anastomosis between the splenic artery and the SMA

3. Interposition graft, using a segment of donor internal or external iliac artery between the splenic artery and the SMA

After pancreas-kidney procurement, if the celiac axis and SMA have been procured with the pancreas (aortic Carrel patch), no further dissec- tion or vascular reconstruction is done.

When venous reconstruction is necessary, the portal vein is only rarely lengthened, because we believe that a short portal vein decreases the risk of venous thrombosis by kinking or impingement.
If necessary, the portal vein extension graft is created using a segment of donor iliac vein, which is anastomosed end-to-end to the donor portal vein.

**Recipient operation** (12). The pancreas graft is usually placed intra-abdominally in the right side of the pelvis for two reasons: dissection of the common iliac vessels is easier compared with the left side and the natural position of the right iliac vessels, which is vein lateral to the artery, does not require vascular realignment, though on the left side it might.

The common, external, and internal iliac arteries are completely mobilized; for right-sided dissections the cecum is mobilized. For complete mobilization of the vein, we pay particular attention to division of all internal iliac veins. After the bladder is mobilized, nonuremic recipients are systemically heparinized.

For the inflow vessel we generally use the common or external iliac artery. Alternatively, the internal iliac artery, the aorta, or the inferior mesenteric artery can be used. If the graft is placed on the right side, the iliac vein remains lateral to the iliac artery. If the graft is placed on the left side, the iliac vein is positioned medial to the iliac artery. For complete mobilization of the vein, the internal iliac artery is ligated and divided. Vascular clamps are placed proximally and distally onto the iliac vasculature. A venotomy and (more proximally) an arteriotomy are then performed. Four stay sutures are placed in the arterial wall for intimal flaps are tacked at this point. The head of the pancreas is oriented in a caudad direction and the tail is oriented in a cephalad direction. Vascular anastomoses are created using running 6-0 Prolene sutures for the arterial and venous anastomoses. Before unclamping, the pancreas graft is reperfused with 25 g of mannitol given intravenously to the recipient.

Next, the duodenocystostomy is created. It is either hand-sewn (two-layer technique using polydioxanone for the inner and Prolene sutures for the outer layer) or done with the end-to-end anastomosis stapler (13). The duodenocystostomy is done between the antimesenteric lateral aspect of the duodenum and the posterior-superior aspect of the bladder dome. The open distal duodenal end is shortened (leaving about 10 cm of graft duodenum), and the stump is stapled, oversewn, and inverted.

After the recipient operation is completed, the abdominal cavity is irrigated with a total of 4 L of solution containing cephalothin sodium (1,000 mg/L) and amphotericin B (10 mg/L). Usually, no drains are inserted.

**General postoperative care** (14). Postoperatively, blood glucose levels are determined at the bedside at least every 2 hours. Insulin is administered intravenously, as needed, to keep blood sugar levels < 150 mg/dL during the first 14 days after the transplant. For intravenous fluid requirements < 300 mL/hr, D5W 0.5 normal saline plus 10 mEq NaHCO3/L is given; for intravenous fluid requirements > 300 mL/hr, D1W 0.5 normal saline plus 10 mEq NaHCO3/L. For all recipients, a nasogastric tube is placed at the time of transplant and is discontinued when the postoperative ileus resolves, usually between day 5 and 7. At that time, a clear liquid diet is started, which is advanced to a regular diet by the time of hospital discharge, usually by day 15.

Generally, recipients take acetylsalicylic acid (162 mg/day orally) for the first year after the transplant.

**Antimicrobial prophylaxis and treatment** (8). Perioperatively, all recipients in our series were given antimicrobial prophylaxis. They received imipenem-cilastatin (Primaxin, Merck & Co. Inc., West Point, PA) alone (500 mg intravenously) or imipenem-cilastatin plus vancomycin (Vancocin, Eli Lilly & Co., Indianapolis, IN) (1,000 mg) at the time of anesthetic induction and for 7 days after the transplant. Antimicrobial prophylaxis was adjusted according to the results of duodenal culture. One double-strength tablet per day of trimethoprim-sulfamethoxazole (Bactrim, Hoffmann-LaRoche, Inc., Nutley, NJ) was routinely administered in the absence of documented allergy to sulfonamides.

**Antifungal prophylaxis**, implemented in August 1991, consisted of fluconazole (Diflucan, Roerig Division, Pfizer Inc., New York, NY) (400 mg/day intravenously), at the time of anesthetic induction and for 7 days after the transplant. Postoperative nystatin swish and swallow (Nilstat, Lederle, Standard Products, Wayne, NJ) or clotrimazole (Mycelex, Troches, Bayer Pharmaceuticals, West Haven, CT) was administered indefinitely to reduce fungal colonization of the gastrointestinal tract.

**Antiviral prophylaxis**, as part of a controlled trial, was administered to prevent infection secondary to cytomegalovirus and other herpes viruses. It consisted of acyclovir (Zovirax, Glaxo Wellcome Inc., Research Triangle Park, NC) or ganciclovir (Cytovene, Roche Laboratories, Nutley, NJ).
Immunosuppression (4). Prednisone (2 mg/kg/day) was initiated intraoperatively for all recipients and was tapered to 0.25 mg/kg/day by 6 months after the transplant. Azathioprine (Imuran, Glaxo Wellcome Inc.) (2.5 mg/kg/day) was given intravenously during the operation and continued orally (2.5 mg/kg/day) indefinitely if the white blood cell count was 3,000 cells/mm$^3$ or more. Beginning on the day after the operation, a 7- to 14-day induction course of Minnesota antilymphocyte globulin, or, after 1992, antithymocyte globulin (both 20 mg/kg/day intravenously) or OKT3 (Orthoclone OKT3, Ortho Biotech Inc., Raritan, NJ) (5 mg/kg/day intravenously) was administered.

PAK and PTA recipients were given cyclosporine A (CsA) (Sandimmune, Sandoz Pharmaceuticals, East Hanover, NJ) (3 mg/kg/day intravenously) during the operation and continuing for 5 to 7 days until oral administration was possible. SPK recipients were given CsA (8 mg/kg/day orally) beginning on day 5. If the kidney allograft dysfunctioned, the introduction of CsA was delayed until function was adequate or until the antibody induction course was completed.

For all recipients, maintenance therapy consisted of prednisone, azathioprine, and CsA. CsA levels were adjusted during the induction and maintenance phases to achieve whole blood levels of 200 to 250 ng/mL for the first 6 months, 150 to 200 ng/mL for the second 6 months, and 100 to 150 ng/mL thereafter, using high-pressure liquid chromatography.

Rejection: diagnosis and treatment (4). Pancreas rejection after solitary bladder-drained transplants was defined by a decrease of urinary amylase levels of 25% or more from baseline on two consecutive measurements or by diagnosis from a biopsy. Rejection after solitary enteric-drained or duct-injected transplants was defined by an increase in serum glucose or serum amylase levels or by diagnosis from a biopsy. Irrespective of the management of exocrine pancreas secretions, rejection after SPK transplants was frequently diagnosed by an increase in serum creatinine levels. Kidney biopsies were obtained whenever rejection was clinically suspected. In general, other causes of graft dysfunction (eg, infection, leak) were ruled out by imaging studies and clinical findings.

Surgical complications. Relaparotomy was defined as any reoperative procedure involving the intra-abdominal space, done during the first 3 months after transplant or during the initial pancreas transplant hospital stay if it exceeded 3 months. Causes of relaparotomy (determined by reviewing preoperative, operative, and postoperative findings) were classified as follows: infection (culture-proved intra-abdominal only), vascular graft thrombosis, anastomotic and duodenal stump leak, pancreatitis, bleeding, and other causes (eg, acute cholecystitis). Relaparotomies were categorized as elective versus nonelective, and nonrelated versus related to the preceding pancreas transplant.

The three most common indications for early relaparotomy—intra-abdominal infection with or without graft pancreatitis, vascular graft thrombosis, and anastomotic and duodenal stump leaks—were studied in detail. Only symptomatic patients with documented culture-positive intra-abdominal infections were included in this study. Cultures were obtained from aspirations guided by computed tomography (CT) or ultrasonography, or at the time of abdominal exploration. Clinical symptoms included fever, purulent wound drainage, ileus, diarrhea, acute abdomen, and sepsis. Thrombosis was diagnosed by clinical symptoms, imaging study results, intraoperative findings, or a combination thereof. Clinical symptoms included graft tenderness, rapidly declining or absent urinary amylase levels, unexplained hyperglycemia, rapidly and unexpectedly increasing insulin requirements, dark hematuria and unexplained hemoperitoneum, leukocytosis, and thrombocytopenia. Imaging studies included color duplex Doppler ultrasonography, pancreas perfusion scintigraphy, CT scan (with intravenous contrast enhancement of the pancreas graft), and arteriography. The thromboses were differentiated (arterial versus venous) based on pre- and intraoperative findings, imaging study results, and the histopathologic report. Anastomotic and duodenal stump leaks after bladder-drained, whole-organ, cadaver donor pancreas transplants were diagnosed by clinical symptoms, imaging study results, laboratory findings, or a combination thereof. Clinical symptoms included abdominal pain, abdominal distention, fever, decreased urine output, peritonitis, and improvement after placement of Foley catheter. Imaging studies included cystogram and CT scan with bladder contrast. Laboratory findings included an increase in serum amylase, decrease in urine amylase, or increase in serum creatinine levels, or a combination thereof. The leaks were differenti-
ated (anastomotic versus duodenal stump) based on pre- and intraoperative findings, as well as imaging study results.

Statistical analysis. Categorical variables were analyzed using the chi-square test, and when applicable, Fisher's exact test. Continuous variables were analyzed parametrically using the t test and nonparametrically using the Mann-Whitney U test.

Pancreas graft and patient survival rates were calculated according to the Kaplan-Meier method. For pancreas grafts, the time of graft loss was determined by return to exogenous insulin use after insulin independence; 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 pancreas and kidney graft loss. Survival rates were compared among groups using the generalized Wilcoxon test. For all univariate statistical tests, p values < 0.05 were considered significant.

Risk factors for graft and patient survival were studied (respectively) in four different regression analyses: all recipients, SPK only, PAK only, and PTA only. Variables included donor age (per 10-year increments), recipient age (per 10-year increments), preservation time, transplant number (primary versus retransplant), recipient category (SPK, PTA, PAK), duration of diabetes (per 10-year increments), transplant year (per 1-year increments), human leukocyte antigen mismatch (number of mismatches), cause of death (cerebrovascular versus traumatic), and risk factors specific to certain surgical complications (e.g., thrombosis after left-sided versus right-sided pancreas graft placement). For all multivariate analyses, p value < 0.15 was considered significant.

Results

Relaparotomy. Relaparotomy was required after 32% of all pancreas transplants. The relaparotomy rate was highest for SPK (56%), followed by PAK (25%) and PTA (16%) (SPK and PAK versus PTA: p < 0.03). Multiple relaparotomies were necessary for 9% of all recipients: 12% for SPK, 9% for PAK, and 4% for PTA (p = NS). The most common indications for relaparotomy were intra-abdominal infection with or without graft pancreatitis, vascular graft thrombosis, anastomotic and duodenal stump leaks, and bleeding. In all three recipient categories, the highest relaparotomy rate was for infection with or without graft pancreatitis. All relaparotomies were nonelective, and all were related to the preceding pancreas transplant. All were done as open operations, with no laparoscopic procedures.

For 84 SPK recipients, 153 relaparotomies (1.8 per recipient) were done; for 35 PAK recipients, 57 were done (1.6); and for 23 PTA recipients, 27 were done (1.2).

The most common reoperative procedures were drainage of intra-abdominal abscess and pancreatic fluid with graft pancreas necrosectomy (a total of 119 relaparotomies: SPK, 84; PAK, 26; PTA, 9); transplant pancreatectomy (a total of 81 relaparotomies: SPK, 42; PAK, 25; PTA, 14); intra-abdominal hemostasis with evacuation of hematoma (a total of 24 relaparotomies: SPK, 13; PAK, 7; PTA, 4); and repair of leak at the duodenocystostomy or duodenal stump (a total of 20 relaparotomies: SPK, 13; PAK, 6; PTA, 1).

Patient survival rates at 1 and 5 years with versus without relaparotomy were as follows: for SPK, 77% and 65% versus 87% and 78% (p = 0.04); for PAK, 79% and 76% versus 98% and 81% (p = 0.02); for PTA, 80% and 74% versus 95% and 70% (p = 0.03) (Figs. 1–3).

Graft survival rates at 1 and 5 years with versus without relaparotomy were as follows: for SPK, 32% and 20% versus 82% and 70% (p = 0.0001); for PAK, 11% and 11% versus 71% and 38% (p = 0.0001); for PTA, 26% and 8% versus 60% and 35% (p = 0.0001) (Figs. 1–3).

Overall Cox regression analysis showed that the risk of death was significantly higher for SPK versus PAK (RR = 1.6, p = 0.1) and for SPK versus PTA (RR = 1.9, p = 0.07) recipients. Cox regression analyses showed the following significant risk factors for death: for SPK, older recipient age (RR = 1.4, p = 0.05), retransplant (RR = 2.3, p = 0.05), relaparotomy for infection with or without graft pancreatitis (RR = 2.2, p = 0.03), and relaparotomy for anastomotic leak (RR = 2.3, p = 0.09); for PAK, older recipient age (RR = 2.6, p = 0.01), retransplant (RR = 6.2, p = 0.001), and relaparotomy for thrombosis (RR = 7.6, p = 0.007); for PTA, long preservation time (RR = 3.6, p = 0.01) and relaparotomy for bleeding (RR = 21.7, p = 0.002).

Overall Cox regression analysis showed that the risk of graft loss was significantly higher for PAK versus SPK (RR = 1.8, p = 0.0004) and for PTA versus SPK (RR = 1.8, p = 0.0004) recipients.
Cox regression analyses showed the following significant risk factors for graft loss: for SPK, older donor age (RR = 1.1, p = 0.13), relaparotomy for thrombosis (RR = 22, p = 0.001), and relaparotomy for intra-abdominal infection with or without graft pancreatitis (RR = 3.6, p = 0.0001); for PAK, older donor age (RR = 1.2, p = 0.13), retransplant (RR = 1.5, p = 0.13), relaparotomy for thrombosis (RR = 15, p = 0.0001), relaparotomy for intra-abdominal infection and graft pancreatitis (RR = 9.3, p = 0.004), relaparotomy for anastomotic and duodenal leaks (RR = 5.6, p = 0.007), and relaparotomy for bleeding (RR = 3.6, p = 0.06); for PTA recipients, relaparotomy for thrombosis (RR = 9.4, p = 0.02).

Intra-abdominal infection. Intra-abdominal infection occurred after 20% of all pancreas transplants. Most infections were diagnosed within the first 3 months after the transplant: 61% within the first month, 79% within the first 2 months, and 96% within the first 3 months after the transplant. In 40% of recipients with infections, the diagnosis was made during the initial hospitalization, and 60% were readmitted at various intervals post-transplant. Intra-abdominal infections were generalized (ie, diffuse peritonitis) in 51% and localized in 49%. In 30%, an anastomotic or duodenal stump leak was present; in 30%, transplant pancreatitis. Of recipients with infections, 76% had a functioning graft at the time of diagnosis. Causes of graft failure before intra-abdominal infection occurred were vascular graft thrombosis (14%), rejection (7%), and graft pancreatitis (3%). The incidence of intra-abdominal infection was highest after graft thrombosis: 27% of recipients with vascular graft thrombosis had an intra-abdominal infection.

By recipient category, the rate of intra-abdominal infection was 18% for SPK, 24% for PAK, and 20% for PTA recipients (p = NS). By donor type, the rate was significantly higher for living related donor (42%) versus cadaver donor recipients (18%) (p = 0.001). By duct management technique, the rate was significantly higher for enteric-drained (39%) versus bladder-drained transplants (18%) (p = 0.001). In the SPK category, neither dialysis dependence nor dialysis mode affected the rate; of recipients with infections, 21% were on peritoneal dialysis, 46% on hemodialysis, and 33% not on dialysis at all (p = 0.5).

Of 89 intra-abdominal infections, 48 (54%) were caused by bacterial species only, 13 (15%) by fungal species only, and 28 (31%) by bacterial and fungal species. Of sole bacterial infections, the most common microorganisms were Staphylococcus species; of sole fungal infections, Candida albicans.
infections were most common. *Staphylococcus* species and *C. albicans* were the most common causes of mixed infections. Of note, positive donor duodenal cultures were not associated with increased intra-abdominal infection rates; for recipients with versus those without infection posttransplant, cultures taken from the donor duodenum were positive in 17% versus 18% of cases (p = NS).

Of 89 intra-abdominal infections, 80 (90%) required exploratory laparotomies, 56% required 1 relaparotomy, 29% required 2, and 15% required more than 2. A transplant pancreatectomy was performed in 70% of recipients undergoing relaparotomy. Only 9 (10%) intra-abdominal infections were successfully treated with percutaneous drainage of the peripancreatic abscess.

Pancreas graft loss from intra-abdominal infection was a major risk factor for a subsequent pancreas retransplant. Of 13 pancreas retransplants done after a previous graft loss from infection, 12 (92%) retransplants were again complicated by infection. Of note, 10 of those infections at retransplant were caused by the same microbial species that had caused failure of the previous graft, after an interval of 1–5 years.

Intra-abdominal infection had a significant impact on both patient and graft survival. Overall patient survival at 1 and 3 years was 76% and 74% for recipients with versus 92% and 84% without infection (p = 0.005) (Figs. 4–6). By recipient category, patient survival was significantly lower only for SPK, but not PAK and PTA, recipients. Overall graft survival at 1 and 3 years was 17% and 11% for recipients with versus 63% and 50% without infection (p = 0.0001) (Figs. 4–6). Graft survival was significantly lower for recipients with infection regardless of the recipient category. For SPK recipients, the rate of graft loss from intraabdominal infection was not significantly different for those on peritoneal dialysis versus those on hemodialysis (p = 0.1); but it was higher for those on hemo- or peritoneal dialysis versus those not on dialysis (p = 0.04).

Outcomes after sole bacterial infections was more favorable than after sole fungal or combined fungal and bacterial infections. Graft function continued in 44% of recipients with sole bacterial versus only 22% with sole fungal or combined fungal and bacterial infections (p = 0.03). Graft pancreatectomy was required in 56% of recipients with sole bacterial versus 78% with sole fungal or combined fungal and bacterial infections (p = 0.03). Mortality was 6% for recipients with...
Table 1. Incidence of Vascular Thrombosis by Recipient Category and Donor Type

<table>
<thead>
<tr>
<th>Category and Donor Type</th>
<th>Thromboses</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPK (n = 198)</td>
<td>18 (9/9)</td>
</tr>
<tr>
<td>CAD, whole-organ (n = 196)</td>
<td>18 (9/9)</td>
</tr>
<tr>
<td>CAD, segmental (n = 2)</td>
<td>0</td>
</tr>
<tr>
<td>PAK (n = 102)</td>
<td>21 (9/12)</td>
</tr>
<tr>
<td>CAD, whole-organ (n = 91)</td>
<td>18 (6/12)</td>
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<td>CAD, segmental (n = 1)</td>
<td>0</td>
</tr>
<tr>
<td>LRD, segmental (n = 10)</td>
<td>3 (5/0)</td>
</tr>
<tr>
<td>PTA (n = 158)</td>
<td>14 (4/10)</td>
</tr>
<tr>
<td>CAD, whole-organ (n = 107)</td>
<td>9 (2/7)</td>
</tr>
<tr>
<td>CAD, segmental (n = 10)</td>
<td>1 (1/0)</td>
</tr>
<tr>
<td>LRD, segmental (n = 21)</td>
<td>4 (1/3)</td>
</tr>
</tbody>
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SPK, simultaneous pancreas-kidney transplant; CAD, cadaver donor; PAK, pancreas after previous kidney transplant; LRD, living related donor; PTA, pancreas transplant alone.

Vascular graft thrombosis. The overall incidence of vascular graft thrombosis was 12%; venous vascular graft thrombosis (7%; n = 31) was slightly more frequent than arterial graft thrombosis (5%; n = 22). Thromboses occurred early after transplantation: 47% within 3 days, 70% within 7 days, and 90% within 21 days. The overall thrombosis rate was not significantly different for primary (12%; n = 41) versus retransplant (14%; n = 12) recipients.

By recipient category, vascular graft thrombosis was significantly higher for PAK (21%) versus PTA (10%) and SPK (9%) recipients (p < 0.05) (Table 1). For cadaver donor whole-organ grafts, the rate of vascular graft thrombosis was lowest for PTA recipients (8%). The thrombosis rate was higher for living related donor (23%) versus cadaver donor (11%) recipients, albeit not significantly (p = 0.08). Likewise, the thrombosis rate was higher for living related donor and cadaver donor recipients of segmental (18%) versus whole-organ grafts (11%) (p = 0.2).

By type of vascular pancreas graft reconstruction, the lowest thrombosis rate was after Y-graft reconstruction (10%), and when no arterial reconstruction was required and an aortic Carrel patch was used (10%). This rate was significantly lower than after construction of an end-to-side anastomosis between the splenic artery and SMA (21%) or after placement of an interposition graft between the splenic artery and SMA (16%) (Table 2). Portal vein extension grafts did not increase the incidence of vascular graft thrombosis; 11% of the grafts without versus 15% with portal vein extension grafts thrombosed (p = NS).

By pancreas graft placement, the rate of vascular thrombosis was 9% for medial placement (ie, inflow through the aorta of the inferior mesenteric artery), 10% for right-sided placement, 21% for left medial placement (ie, medial to the sigmoid colon mesentery), and 37% for left lateral placement (ie, lateral to the sigmoid colon mesentery). The difference between left-sided placement versus all other implantation sites was statistically sig-

Table 2. Incidence of Vascular Thrombosis for Whole-organ Cadaver Donor Grafts by Type of Arterial Reconstruction

<table>
<thead>
<tr>
<th>No reconstruction</th>
<th>Y-graft</th>
<th>End-to-side anastomosis</th>
<th>Interposition graft</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPK (n = 196)</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAK (n = 91)</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA (n = 107)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Interposition graft between splenic artery and gastroepiploic artery; superior mesenteric artery anastomosed to recipient inflow vessel.

†End-to-side anastomosis of splenic artery to celiac axis (functional aortic Carrel patch).

SPK, simultaneous pancreas-kidney transplant; PAK, pancreas after previous kidney transplant; PTA, pancreas transplant alone.
nificant (p = 0.01). For living related donor grafts, the thrombosis rate for right-sided placement (16%) was lower versus left-sided or median placement (50%) (Table 3).

Duct management technique (bladder versus enteric drainage), preservation solution (silica-gel-fractionated plasma versus University of Wisconsin solution), and type of recipient arterial inflow vessel (common versus external versus internal iliac artery versus aorta versus other vessels) did not affect the vascular graft thrombosis rate by univariate analysis. Nor did the dialysis status at transplant for SPK recipients; the thrombosis rate was 8% for those on dialysis versus 10% for those not on dialysis.

Patient survival rates were not significantly lower for recipients with versus without vascular graft thrombosis. For SPK recipients, patient survival rates at 1 and 3 years were 91% and 91% with versus 83% and 77% without thrombosis (p = 0.4); for PAK recipients, 86% and 76% with versus 93% and 88% without thrombosis (p = 0.4); for PTA recipients, 83% and 83% with versus 94% and 89% without thrombosis (p = 0.3).

Cox regression analysis showed that PAK recipients had a significantly higher risk for graft thrombosis than SPK recipients (RR = 0.3, p = 0.002). For SPK recipients, significant independent risk factors for graft thrombosis were cardiocerebrovascular cause of donor death (RR = 5.2, p = 0.03), left medial pancreas graft placement (RR = 5.0, p = 0.03), and graft pancreatitis (RR = 12.7, p = 0.001). For PTA recipients, the graft thrombosis risk was increased by older donor age (RR = 1.2, p = 0.05), the use of an interposition graft between the splenic artery and the superior mesenteric artery (RR > 25, p = 0.03), end-to-side anastomosis of the splenic artery and the superior mesenteric artery (RR > 25, p = 0.01), and graft pancreatitis (RR = 7.7, p = 0.17).

Anastomotic and duodenal stump leaks. Anastomotic and duodenal stump leaks occurred after 10% of all bladder-drained, whole-organ, cadaver donor pancreas transplants. Of the 42 duodenal leaks, 29% occurred early (mean, 11 days; range, 1–28 days), and 71% late (mean, 7 months; range, 1–36 months). The site of the leak was the duodenocystostomy site (true bladder anastomotic leaks) in 36%, the stapled proximal duodenal stump in 19%, and the stapled distal duodenal stump in 9%. In the remaining 36%, it was impossible to identify the exact site of the leak because of conservative treatment or indeterminate diagnostic studies (cystogram and CT scan).

The most common symptoms were abdominal pain (88%), abdominal distention (69%), fever (57%), decreased urine output (51%), peritonitis (26%), improvement after placement of a Foley catheter (24%), and vomiting (12%). Serum amylase levels rose in 48%, urine amylase levels decreased in 38%, and serum creatinine levels rose in 33%. The incidence of leaks did not differ by recipient category.

We operated on 30 recipients with leaks (71%). In 23 of them, the leak was oversewn; in 1 the leak

**Table 3. Incidence of Vascular Thrombosis by Graft Placement**

<table>
<thead>
<tr>
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<th>Right side</th>
<th>Left lateral*</th>
<th>Left medialt</th>
<th>Median</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>%</td>
<td>n</td>
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<tr>
<td>SPK (n = 190)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Whole-organ (n = 196)</td>
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<td>0</td>
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<td>0</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Whole-organ (n = 91)</td>
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<td>10</td>
<td>18</td>
<td>5</td>
</tr>
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<td>3</td>
</tr>
<tr>
<td>PTA (n = 138)</td>
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</tr>
<tr>
<td>Whole-organ (n = 107)</td>
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<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Segmental (n = 31)</td>
<td>27</td>
<td>4</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

* Lateral to the sigmoid colon mesentery.
† Medial to the sigmoid colon mesentery.
SPK, simultaneous pancreas-kidney transplant; PAK, pancreas after previous kidney transplant; PTA, pancreas transplant alone.

cause of donor death (RR = 5.2, p = 0.03), left medial pancreas graft placement (RR = 5.0, p = 0.03), and graft pancreatitis (RR = 12.7, p = 0.001). For PTA recipients, the graft thrombosis risk was increased by older donor age (RR = 1.2, p = 0.05), the use of an interposition graft between the splenic artery and the superior mesenteric artery (RR > 25, p = 0.03), end-to-side anastomosis of the splenic artery and the superior mesenteric artery (RR > 25, p = 0.01), and graft pancreatitis (RR = 7.7, p = 0.17).
was already sealed by the time of the operation. In the other 6 recipients, graft pancreatectomy was required because of duodenal blowout in conjunction with graft thrombosis (n = 1), a large perforation of the duodenum and bleeding (n = 1), and peritonitis (n = 4). We treated 12 leaks (29%) conservatively with an indwelling catheter for 1–2 months until resolution.

In 10% leaks recurred 1–5 months after the first leak had been diagnosed. In 2 recipients a bladder anastomosis was converted to enteric drainage; in 1 the duodenocystostomy was taken down with primary bladder closure, resection of the duodenal graft, and ligation of the pancreatic duct; and in 1 the leak was oversewn.

Discussion

The rate of technical failures for pancreas transplants is higher than for any other routinely performed solid organ transplant. Nonimmunologic graft failure, in particular, has hampered more widespread application of solitary pancreas transplants (PTA, PAK). Several factors contribute to surgical complications after pancreas transplants:

1. The underlying disease itself which, for example, makes patients more prone to infections and, in the presence of secondary complications of diabetes mellitus, increases cardiac and cerebrovascular morbidity and mortality peritransplant
2. The transplant procedure, which involves two hollow viscera (duodenum; bladder or intestine)
3. The transplanted organ, with its broad spectrum of potential surgical complications such as pancreatitis, infection, necrosis, pseudocyst, and fistula
4. Extended (compared with kidney or liver transplants) anti-T-cell induction therapy
5. Specific risk factors pertaining to the recipient category, such as uremia in SPK recipients or chronic pretransplant immunosuppression in PAK recipients

For all these reasons, it is not surprising that our overall relaparotomy rate was 32%. This figure is comparable to the relaparotomy rate reported by other pancreas transplant centers, such as the Iowa group (28%) and the Nebraska group (36%) (15, 16). The Wisconsin group reported an overall surgical complication rate of 31%, the majority requiring relaparotomy (24%) (17). By recipient category, our relaparotomy rate was significantly higher for SPK and PAK (versus PTA) recipients. This finding reflects the technically more demanding dual-organ transplant procedure for uremic or preuremic SPK recipients, and the preexisting chronically immunosuppressed state of PAK recipients. Likewise, the rate of multiple relaparotomies was higher for SPK and PAK (versus PTA) recipients.

Relaparotomy for surgical complications had a significant impact on patient and graft survival rates. Both were significantly lower at 1 and 5 years after transplant for recipients with versus without relaparotomy, irrespective of the recipient category. Multivariate analysis showed that the risk of death was significantly higher for SPK and PAK (versus PTA) recipients. Cox regression analyses showed that for SPK recipients, relaparotomy for infection or anastomotic leak increased the risk of death; for PAK recipients, relaparotomy for thrombosis; and for PTA recipients, relaparotomy for bleeding.

The most significant risk factors for graft survival by recipient category were relaparotomy for thrombosis or infection (SPK) and relaparotomy for thrombosis (PTA). For PAK recipients, relaparotomy for any cause was associated with a higher risk of graft loss, which again can be explained by their long standing chronic pretransplant immunosuppression.

The impact of relaparotomy on perioperative morbidity and mortality includes an increase in median hospital charges: for SPK recipients, by $65,700; for PAK recipients, by $45,100; and for PTA recipients, by $35,800. Thus, the cost of a pancreas transplant with (versus without) relaparotomy was increased by 65% for SPK, 59% for PAK, and 46% for PTA recipients. In fact, in a previous analysis, we showed that relaparotomy was the most important risk factor for an increase in hospital charges (18).

The most frequent indications for relaparotomy in our series were intra-abdominal infection, vascular graft thrombosis, and anastomotic and duodenal leaks (19). This finding is in line with previous reports from other pancreas transplant centers (15–17), but we were interested in the specific impact on patient and graft outcome of each of these indications.

Intra-abdominal infection occurred after 20% of all pancreas transplants. We have recently reported on contributing factors, such as postreper-
fusion pancreatitis and peripancreatitis (with local release of proinflammatory substances, providing an optimal environment for growth of microorganisms), contamination of the donor duodenum, microbial translocation through the duodenal wall, prolonged duration of surgery, perioperative immunosuppression, underlying disease, and surgical complications (9). Our infection rate is comparable to reports from the Wisconsin group (17%) and the Iowa group (18%) (15, 20).

In our series, at the time of diagnosis, only 76% of recipients with infections still had a functioning graft. We noted a particularly high incidence of infection after graft pancreatectomy for thrombosis (27%). Interestingly, transplant pancreatitis was diagnosed in 30% of recipients with infections, although it is difficult to retrospectively analyze which came first, graft pancreatitis with subsequent infection or perigraft infection with subsequent pancreatitis. Intra-abdominal infection was the most common indication for single or multiple relaparotomies and the second most common indication for graft pancreatectomy. It had a more significant impact on costs than any other surgical complication.

By recipient category, we found a slightly higher rate of infection for PAK recipients. This finding matches the previous report by the Nebraska group (17). It can be explained by the long-term chronic immunosuppressed state of PAK recipients. As with our first experience with intra-abdominal infections that we reported 10 years ago, the infection rate in this series was again higher for enteric-drained (39%) versus bladder-drained (18%) transplants (21). The rate was also higher for living related donor recipients (42%), most of whom had enteric-drained transplants, versus cadaver donor recipients (18%), most of whom had bladder-drained transplants. For SPK recipients, the infection rate was not different for recipients on hemo- or peritoneal dialysis versus those not on dialysis (22). Thus, recipients on peritoneal dialysis should not be excluded from intraperitoneal pancreas graft placement.

One of our concerns regarding the microbiology of intra-abdominal infection was not confirmed in our retrospective review: positive donor cultures were not associated with an increased infection rate (23). This finding may reflect the facts that recipients were prophylactically on antibiotics for 7 days and that antibody coverage was changed according to sensitivity test results. Duodenal culture results appear to be useful for determining the length, specificity, and microbial target of perioperative antimicrobial prophylaxis.

In our series, 90% of recipients with infections required exploratory laparotomy; of these, 45% underwent multiple relaparotomies and 70% an eventual graft pancreatectomy. As previously shown, pancreatic graft loss resulting from infection was the major risk factor for a pancreas retransplant; most pancreas retransplants done after the previous graft was lost owing to infection were again complicated by infection (24). The infections were caused by the same microbial species, even though the retransplants were done 1–5 years after the first transplant. Do these microorganisms survive dormantly in the abdominal cavity for such long asymptomatic periods and then become active again at the time of retransplant when immunosuppression is restarted? We did not find any intra-abdominal abscesses, but sensitivity test results were identical for microbial species causing intra-abdominal infections after the first transplant and after the retransplant. This finding suggests that these microorganisms persist even after the first infection resolves clinically.

The overall incidence of just fungal and combined fungal and bacterial infections in our series was 46%. It is known from nontransplant surgery that the pancreas is particularly susceptible to fungal infections; the reported infection rate is 23% after pancreatic surgery for benign diseases (25). Yet we noticed a marked difference in outcomes after fungal versus bacterial infections (8). Graft pancreatectomy was required in 78% of recipients with sole fungal, or combined fungal and bacterial, infections versus 56% of recipients with sole bacterial infections. Furthermore, mortality was 20% for recipients with fungal, or combined fungal and bacterial, infections versus 6% with sole bacterial infections.

Infections significantly decreased overall patient and graft survival at 1–3 years posttransplant. Patient survival rates by recipient category were significantly lower only for SPK recipients, but not for PAK or PTA recipients. Yet graft survival was significantly lower regardless of the recipient category.

Of note, for SPK recipients, the rate of graft loss owing to infection was higher for those on (hemo- or peritoneal) dialysis than for those not on dialysis. This is again a strong argument for preemptive SPK transplants in an attempt to decrease peritransplant morbidity and overall costs.
If we compare the results of our current analysis with our first experience with infections published 10 years ago, we must admit that, despite improvements in surgical technique and perioperative care, the incidence of infections has not changed. But the percentage of recipients who recover from infection with graft function has increased from 19% to 34%, and the mortality rate has decreased from 27% to 12%. Reasons may include greater experience in routinely managing this (frequent) complication and increased vigilance, leading to earlier diagnosis and treatment.

Next to intra-abdominal infection, vascular graft thrombosis was the most common indication for relaparotomy. For graft pancreatectomy, vascular graft thrombosis was the most common indication. This finding is in line with IPTR data showing that thrombosis accounts for almost 60% of all nonimmunologic graft failures (2). In our series, the overall incidence of vascular graft thrombosis was 12%. This incidence is comparable to reports from other centers, where graft thrombosis ranges between 10% and 39% (26-29). Only the Wisconsin group has consistently reported a < 1% incidence, but for SPK recipients only (30).

In our series, PAK recipients had a thrombosis rate twice as high (21%) as PTA (10%) or SPK (9%) recipients. A higher thrombosis rate for PAK recipients (39%) was also reported by the Nebraska group (29). One might speculate that, in this category, either the long-term chronic immunosuppression required for the kidney transplant unfavorably alters the recipient's coagulatory system (owing to the procoagulant effects of CsA and prednisone) or the technical adaptations and modifications (in light of a right-sided kidney transplant) required for the subsequent pancreas transplant increases the risk of thrombosis. We also observed a higher thrombosis rate for segmental graft recipients. Although flow through the splenic artery and vein does not differ for segmental versus whole-organ grafts, the shorter splenic artery and vein in segmental grafts allow for less flexibility and are more prone to bending or twisting. In addition, the transverse pancreatic artery, which supplies the body and the tail of the pancreas, and which receives collateral flow from the SMA (31), is not revascularized in segmental grafts. Thus, the blood supply of the segmental graft is critically dependent on the splenic artery; any partial or complete thrombosis would be more detrimental than for whole-organ grafts. The advantage of the dual blood supply of the whole-organ graft has also been shown for recipients with stable graft function: even with clinically occult thrombosis of the SMA or the splenic artery, documented on angiogram, their graft function was maintained by collateral flow (32). It is therefore not surprising that the thrombosis rate for segmental grafts was twice that of cadaver donor grafts.

We also observed that the type of arterial reconstruction affected the incidence of thrombosis. The lowest thrombosis rate was after Y-graft reconstruction or when an aortic Carrel patch was used. When the end-to-side anastomosis or interposition graft techniques were used, the rates were significantly higher, most likely owing to less spatial flexibility than with a Y-graft or owing to preexisting donor arteriosclerotic disease (ie, when the donor Y-graft could not be used for that reason). In contrast to arterial reconstruction, portal vein reconstruction (ie, extension grafts) had no impact on the incidence of thrombosis.

Another important risk factor for thrombosis was the implantation site. Usually, the side of choice is the right iliac system, with complete mobilization of the right iliac vein, which allows creation of a tension-free venous anastomosis lateral to the arterial anastomosis (12); however, when the previous kidney graft has been placed in the right side or with a retransplant, the left iliac system or the aorta has to be used. On the left side, the sigmoid colon is in the way, and the graft has to be positioned either medially (ie, onto the common iliac artery) or laterally (ie, onto the external iliac artery). The left common iliac vein is tethered by the internal iliac artery and is much more posterior than its right counterpart. This explains the thrombosis rate of 10% for right-sided placement versus 21% for left medial placement and 37% for left lateral placement for cadaver donor grafts. Likewise, for living relative-donated grafts, the thrombosis rate was 16% for right-sided versus 50% for left-sided placement (11). Interestingly, median placement (ie, the aorta) had a low risk of graft thrombosis; it should be considered for patients in whom left-sided placement appears difficult. In our experience, cross-clamping of the distal abdominal aorta or the proximal iliac artery has never had any detrimental consequences for kidney grafts located distally to the temporary occlusion (such as for PAK recipients) (11). But strong consideration must be given to left-sided
with versus without anastomotic or duodenal leaks.

We have confined this retrospective analysis to the most serious surgical complications after pancreas transplants. But other surgical complications deserve a brief mention.

Graft pancreatitis and graft peripancreatitis are most common for recipients with intra-abdominal infection or vascular graft thrombosis. Complications of graft pancreatitis include pancreatic abscess, pancreatic necrosis, perigraft infection, sterile pancreatic and peripancreatic fluid collections, and pseudocyst. Graft pancreatitis can be related to donor risk factors (hemodynamic instability, vasopressor administration), procurement injury, perfusion injury (excessive amounts of flush volume or perfusion pressure), preservation injury, and reperfusion injury. Vasoconstriction, intravascular coagulation, and increased endothelial permeability may result in pancreatic edema, which, in turn, can impair venous drainage. With pancreatic microcirculation progressively impaired, graft thrombosis can result.

Superficial wound infections usually require reexploration only in combination with deep (ie, intra-abdominal) infections (35, 36). We previously reported an 18% incidence of superficial wound infections; 45% were in combination with deep wound infections. We identified prolonged operating time, enteric drainage, and older donor age as risk factors for superficial infection. The microbiologic spectrum was almost identical to that of intra-abdominal infections.

Complications of subsequent pancreas transplant-specific procedures have been detailed elsewhere. To diagnose rejection, we routinely perform CT-guided percutaneous biopsy; if technically not possible (eg, overlying bowel), we alternatively perform transcystoscopic or laparoscopic biopsy (4, 7). Of 75 recipients who underwent percutaneous biopsy, only 1 needed surgical exploration for bleeding (37); of the 83 recipients who underwent transcystoscopic or laparoscopic biopsy, none needed exploration. For graft biopsies, surgical complications after bladder-to-enteric conversion have been rare (38).

Conclusions

Donors must be appropriately selected with regard to age and cause of death. Older donor age was a risk factor for intra-abdominal infection, vascular
graft thrombosis, anastomotic or duodenal leaks, and relaparotomy. Donors over 45 years of age should not be routinely used, particularly if their cause of death is cardio-cerebrovascular disease (39). Accepting older donors to improve HLA-matching cannot be recommended; the tradeoff is a higher graft loss rate and, even more important, a higher mortality rate.

Second, recipients over 45 years of age and those with a history of coronary disease (myocardial infarction, coronary bypass, or angioplasty) should be considered for a kidney transplant alone, rather than an SPK transplant. Previously (9, 39), and again in this analysis, we showed that older recipient age not only has a negative impact on technical failure, but also on patient and graft survival rates. Recipients with preexisting cardiac disease have a significantly higher risk of dying from cardio-cerebrovascular complications (with a functioning graft) than recipients without cardiac risk factors. Patients with advanced diabetic nephropathy should undergo their SPK transplant before dialysis is initiated (ie, preemptively). This policy minimizes dialysis-related complications, as well as intra-abdominal complications and their disastrous consequences. Recipients who were not on dialysis before the transplant were not at higher risk for graft thrombosis.

Third, meticulous surgical technique during graft procurement, preparation, and implantation is paramount. During the donor operation, unnecessary mechanical trauma and excessive perfusion pressures and flush volumes must be avoided. For reconstruction of the arterial pancreas inflow, the Y-graft technique should be used. Intra-peritoneal placement of the pancreas on the right side and the kidney on the left (SPK) is now standard. Diabetic kidney recipients who are candidates for a subsequent pancreas transplant (PAK) should undergo a left-sided kidney transplant. During the pancreas recipient operation, minimal mechanical manipulation of the graft will decrease the likelihood of infection, pancreatitis, and bleeding. The duodenocystostomy and the closure of the duodenal stumps must be done meticulously, without any technical shortcuts or compromises, to minimize leaks and their adverse consequences.

Fourth, for pancreas graft-related complications requiring relaparotomy, the focus must switch from graft salvage to life preservation. Graft pancreatectomy should be done when thrombosis occurs or when clinically symptomatic intra-abdominal infection with or without graft pancreatitis develops. If a leak or bleeding requires relaparotomy, surgical correction should only be considered if the site can easily be identified at the time of relaparotomy, if it can be safely repaired, and if there are no other concurrent complications such as infection. If surgical correction of a leak or bleeding is attempted, the risk of a relaparotomy must be weighed against the increased risk of graft loss and death, particularly for SPK and PAK recipients. In contrast to graft-related complications, other intra-abdominal complications such as acute cholecystitis can be surgically managed without increased risk of graft loss and death.

Fifth, more effective strategies to avert intra-abdominal infections need to be developed. We previously showed that prophylactic antifungal therapy with intravenous fluconazole can reduce the incidence of intra-abdominal fungal infections (8) associated with a significantly higher morbidity and mortality than sole bacterial infections. We are currently investigating the role of continuous irrigation and suction systems for recipients with intra-abdominal infection and graft pancreatitis. If infection can be eradicated by such treatment, graft pancreatectomy could be avoided and mortality reduced. Our efforts continue to focus on strategies that ultimately improve prophylaxis and treatment of intra-abdominal infection, which over the years has remained the most common complication after pancreas transplants.

Sixth, surgical complications requiring relaparotomy cover a broad spectrum of procedures (involving the vascular, hepatobiliary, gastric, intestinal, and urinary tract systems and the grafts themselves). Thus, pancreas transplant surgeons must be prepared to handle adequately surgical complications in diverse areas. Timely diagnosis and knowledge of potential complications, along with expeditious treatment and relaparotomy, are the cornerstones of successful management of surgical complications.

By applying these principles, pancreas graft survival rates should exceed 75% at 1 year posttransplant. Future research may reduce the incidence and consequences of surgical complications, so that pancreas transplantation can be more widely applied to nonuremic diabetic patients and can become an option for uremic high-risk type I insulin-dependent patients who are currently not considered for this procedure. Furthermore, more efficient yet less toxic immunosuppressants might decrease not only the rate of immunologic graft failure but also the incidence of surgical complications. It remains to be seen
if the two new immunosuppressants currently used for pancreas transplantation, tacrolimus and mycophenolate mofetil (40, 41), will ultimately help decrease the risk of surgical complications.

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