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Decreased Surgical Risks of Pancreas Transplantation in the Modern Era

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Objective
To document the decreased incidence of surgical complications after pancreas transplantation in recent times.

Summary Background Data
Compared with other abdominal transplants, pancreas transplants have historically had the highest incidence of surgical complications. However, over the past few years, the authors have noted a significant decrease in the incidence of surgical complications.

Methods
The authors studied the incidence of early (<3 months after transplant) surgical complications (e.g., relaparotomy, thrombosis, infections, leaks) after 580 pancreas transplants performed during a 12-year period. Patients were analyzed and compared in two time groups: era 1 (June 1, 1985, to April 30, 1994, n = 367) and era 2 (May 1, 1994, to June 30, 1997, n = 213).

Results
Overall, surgical complications were significantly reduced in era 2 compared with era 1. The relaparotomy rate decreased from 32.4% in era 1 to 18.8% in era 2. Significant risk factors for early relaparotomy were donor age older than 40 years and recipient obesity. Recipients with relaparotomy had significantly lower graft survival rates than those without relaparotomy, but patient survival rates were not significantly different. A major factor contributing to the lower relaparotomy rate in era 2 was a significant decrease in the incidence of graft thrombosis; the authors believe this lower incidence is due to the routine use of postoperative low-dose intravenous heparin and acetylsalicylic acid. The incidence of bleeding requiring relaparotomy did not differ between the two eras. Older donor age was the most significant risk factor for graft thrombosis. The incidence of intraabdominal infections significantly decreased between the two eras; this decrease may be due to improved prophylaxis regimens in the first postoperative week.

Conclusions
Although a retrospective study has its limits, the results of this study, the largest single-center experience to date, show a significant decrease in the surgical risk associated with pancreas transplants. Reasons for this decrease are identification of donor and recipient risk factors, better prophylaxis regimens, refinements in surgical technique, and improved immunosuppressive regimens. These improved results suggest that more widespread application of pancreas transplantation is warranted.

Although pancreas transplantation has gained significant popularity during the past 15 years, it has had the highest surgical complication rate of all routinely performed solid organ transplants. A significant number of pancreas grafts are lost early after transplant secondary to these surgical complications. This high graft loss rate and the morbidity associated with these surgical complications have been major factors in limiting the widespread application of pancreas transplantation. At our center, however, we have noticed a steady decrease in the incidence of these complications. Reasons for this decrease include improved donor and recipient selection criteria, refinements in surgical technique, better immunosuppression, and more effective prophylaxis regimens.

The purposes of this study were to document our improved results and to determine risk factors for complications. We studied the incidence of early surgical complications (those occurring in the first 3 months after the transplant) after all bladder-drained pancreas transplants

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Table 1. DEMOGRAPHIC DATA

	Era 1	Era 2	*P* Value
Total transplants (n)	367	213	—
Category (n, %)	187/88/92	100/80/33	NS
SPK/PAK/PTA	51%/24%/25%	47%/37%/16%	
Mean recipient age (yrs)	36.5	39.7	NS
Mean donor age (yrs)	32.8	27.2	.04
Years diabetic	24.0	25.2	NS
% Retransplants	14.6%	12.2%	NS
% Cadaver donors	92.1%	89.7%	NS

SPK, simultaneous pancreas and kidney, PAK, pancreas after kidney; PTA, pancreas transplant alone.

performed at our center during a 12-year period. We hope that documenting the increased safety of pancreas transplantation will provide more support for its widespread application; currently, it remains the only cure for type 1 diabetes mellitus.

PATIENTS AND METHODS

Between June 1, 1985, and June 30, 1997, 580 bladder-drained pancreas transplants were performed at the University of Minnesota. Recipients were analyzed in two time groups: era 1 (June 1, 1985, to April 30, 1994) and era 2 (May 1, 1994, to June 30, 1997). There were 367 recipients in era 1 and 213 in era 2. Transplant categories (SPK, simultaneous pancreas and kidney; PAK, pancreas after kidney; PTA, pancreas transplant alone) were proportionately the same between the two eras (Table 1). The donor operation, which did not change significantly between the two eras, has been detailed previously.[1] The recipient operation underwent some minor modifications in era 2. Specifically, almost all era 2 transplants involved a donor iliac artery Y-graft for the arterial reconstruction, and the pancreas graft was placed on the right side of the abdomen.[2] Only bladder-drained grafts were analyzed, because the vast majority of transplants in both eras were bladder-drained. Donor and recipient selection criteria have been detailed previously.[3]

Immunosuppression

All recipients in both eras received induction therapy, which included an antilymphocyte preparation. Maintenance immunosuppression in era 1 consisted of cyclosporine, azathioprine, and prednisone.[4] Our immunosuppressive protocols changed in 1994, so most era 2 recipients received a triple regimen of tacrolimus, mycophenolate mofetil, and prednisone. During the first 6 months after the transplant, tacrolimus doses were adjusted to maintain serum levels of 10 to 15 ng/mL, then 8 to 10 ng/mL thereafter.

Rejection

Pancreas graft rejection after solitary bladder-drained transplants was defined by a decrease in urinary amylase levels of 25% or more from baseline on two consecutive measurements, or by diagnosis from a biopsy.[4] Pancreas graft rejection after SPK transplants was frequently diagnosed by an increase in serum creatinine levels; kidney biopsies were obtained whenever kidney graft rejection was clinically suspected. Treatment was generally with a course of antilymphocyte therapy.

Prophylaxis

Recipients in both eras received antiviral prophylaxis (acyclovir or ganciclovir) and antibacterial prophylaxis with a broad-spectrum antibiotic (imipenem, ampicillin/sulbactam, or ceftazidime).[5] In addition, recipients in era 2 were also given fluconazole as antifungal prophylaxis for the first week after the transplant. In 1994, we initiated a standard prophylaxis regimen against vascular thrombosis. Therefore, most era 2 recipients received low-dose intravenous heparin (300–500 units/hour) for the first 5 days after the transplant and acetylsalicylic acid (ASA; 325 mg/day) for the first 3 months after the transplant.

Surgical Complications

Relaparotomy was defined as any reoperative procedure involving the intraperitoneal or retroperitoneal space performed during the first 3 months after the transplant or during the initial pancreas transplant hospital stay, if it exceeded 3 months.[6,7] Causes of relaparotomy (determined by reviewing preoperative, operative, and postoperative findings) were classified as vascular graft thrombosis, intra-abdominal infection, bleeding, anastomosis and duodenal stump leak, or other. Thrombosis was diagnosed by clinical symptoms, imaging study results, intraoperative findings, or a combination thereof. Bleeding was defined as a significant complication if it necessitated a reoperation. Only symptomatic patients with documented culture-positive intraabdominal infections were included in this study. Cultures were obtained from aspirations guided by computed tomography or ultrasonography, or at the time of abdominal exploration. Anastomotic and duodenal stump leaks were diagnosed by clinical symptoms, imaging study results, laboratory findings, or a combination thereof.

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. Pancreas graft and patient survival rates were calculated according to the Kaplan-Meier method. Pancreas graft loss was defined by return to exogenous insulin use after insulin

Table 2. INCIDENCE AND REASONS FOR RELAPAROTOMY

	Era 1	Era 2	*P* Value
Total transplants (n)	367	213	—
Relaparotomy rate	32.4%	18.8%	.001
Reasons for relaparotomy:			
Thrombosis	10.1%	5.6%	.06
Infections	12.0%	3.8%	.001
Bleeding	4.9%	6.6%	.14
Leaks	3.8%	6.1%	NS
Other	6.5%	1.3%	.001

independence. Calculation of patient survival included death occurring after pancreas and kidney graft loss. Survival rates were compared among groups using the generalized Wilcoxon test. $P < .05$ was considered significant.

Also, using univariate techniques, we studied risk factors for poor graft survival, relaparotomy, thrombosis, and intraabdominal infections specifically in era 2 recipients. Variables included donor age, recipient age, recipient body-mass index, preservation time, transplant number (primary vs. retransplant), recipient category (SPK, PTA, PAK), duration of diabetes, and pretransplant dialysis status.

RESULTS

Demographic data for recipients in era 1 and era 2 are shown in Table 2. We found no significant difference between the two eras in the number of recipients in each transplant category (SPK vs. PAK vs. PTA). SPK transplants constituted roughly half of all transplants in both eras. PAK transplants were slightly more common in era 2, but the difference was not statistically significant. The two eras also did not differ with respect to mean recipient age, number of years the recipient was diabetic before the transplant, or the proportion of repeat transplants. However, mean donor age differed significantly (33 years in era 1, 27 years in era 2; $P = .04$).

Relaparotomy

Relaparotomy rates (total and broken down by reason for relaparotomy) are shown in Table 2. The percentage of recipients requiring early relaparotomy significantly decreased (32.4% in era 1, 18.8% in era 2; $P = .001$). The death rate in recipients requiring early relaparotomy also decreased significantly (9% in era 1, 4% in era 2; $P = .05$). The decreased relaparotomy rate was not noted until the start of era 2; when era 1 recipients were subdivided into those who underwent transplantation before 1990 versus between 1990 and 1994, no significant difference was noted in the relaparotomy rate (26.2% vs. 35.8%, P = NS).

The two main reasons for the lower relaparotomy rate in era 2 are a lower incidence of graft thrombosis and a lower number of intraabdominal infections requiring reoperation. Bleeding complications were slightly more common in era 2, but the difference was not statistically significant. The incidence of leaks was similar between the two eras. Other causes for relaparotomy in era 1 included fascial wound dehiscence (n = 5), pseudoaneurysm of the iliac artery (n = 2), kidney graft thrombosis (n = 1), colonic perforation (n = 4), acute cholecystitis (n = 11), and a negative exploration (n = 1). In era 2 there were only three relaparotomies for other causes: fascial wound dehiscence (n = 2) and pseudoaneurysm of the iliac artery (n = 1). Overall, the incidence of relaparotomy secondary to other causes was higher in era 1 than era 2 (6.5% vs. 1.4%, $P = .01$).

To identify risk factors for relaparotomy, we performed a univariate analysis for the 213 era 2 recipients. Most significant were older donor age (older than 40 years, 35.1%; 40 years or younger, 11.0%; $P = .002$) and recipient obesity (body-mass index >25 kg/m^2, 25.3%; ≤ 25 kg/m^2, 14.3%; $P = .04$). Older donor age was associated with a significantly higher incidence of graft thrombosis and intraabdominal infections in the recipient. Recipient obesity was also associated with an increased risk for thrombosis (9.2% vs. 4.0%, $P = .10$), although this did not quite reach statistical significance. Other surgical complications such as leaks (9.2% vs. 7.9%, P = NS) and intraabdominal infections (10.3% vs. 4.7%, $P = .10$) also tended to be more common in obese recipients, but again the differences did not reach statistical significance.

Not associated with an increased risk for relaparotomy were recipient age, duration of diabetes, type of dialysis, cause of donor death, preservation time, transplant number, or graft location. We looked at acute rejection specifically to determine whether it increased the likelihood of a surgical complication. The overall incidence of relaparotomy in recipients with acute rejection was 15.1% compared with 20.0% in those without acute rejection (P = NS). Major surgical complications (e.g., thrombosis, bleeding, infections, and leaks) were not increased in the presence of acute rejection.

Patient and graft survival rates for era 2 recipients requiring versus not requiring relaparotomy are shown in Figure 1. Graft survival rates were significantly lower for recipients requiring relaparotomy. Approximately 40% of relaparotomies resulted in graft pancreatectomy. Reasons for pancreatectomy included vascular thrombosis with infarction of the graft, diffuse intraabdominal infections (usually in conjunction with leaks), and severe graft pancreatitis. Of note, however, patient survival rates did not significantly differ between recipients requiring versus not requiring relaparotomy. Also, graft survival in recipients requiring relaparotomy was significantly better in era 2 than era 1: 44% in era 2 versus only 25% in era 1 ($P = .01$) at 1 year after the transplant.

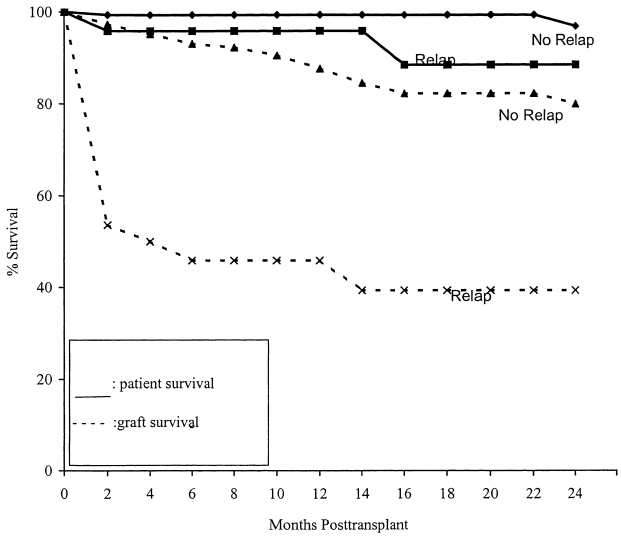

Figure 1. Patient and graft survival rates for recipients requiring versus not requiring relaparotomy (era 2 only).

Vascular Thrombosis

The overall incidence of vascular graft thrombosis significantly decreased (12.1% in era 1, 5.8% in era 2; $P = .02$). The majority (70%) of era 2 recipients received thrombosis prophylaxis with heparin and ASA compared with fewer than 5% of era 1 recipients. The incidence of bleeding complications requiring relaparotomy slightly increased with the routine use of heparin (4.9% in era 1, 6.6% in era 2; $P = .14$), although this difference did not reach statistical significance. Graft thrombosis always resulted in graft pancreatectomy. However, relaparotomy for bleeding never resulted in graft pancreatectomy; graft survival after the transplant was no different in recipients who underwent exploration for bleeding compared with recipients with no significant bleeding (Fig. 2).

Univariate analysis for the 213 era 2 recipients found older donor age to be the most significant risk factor for graft thrombosis. As donor age increased, so did the incidence of thrombosis: it was 1.8% for those younger than 20 years, 3.7% for those 20 to 40 years, and 16.2% for those older than 40 years ($P = .009$). Other significant risk factors were related to thrombosis prophylaxis regimens and pretransplant dialysis status. Recipients who received heparin and ASA for prophylaxis after surgery had a 4.0% incidence of thrombosis; the incidence was 10.8% in those who did not ($P = .06$). Recipients receiving dialysis before the transplant had a significantly lower incidence of thrombosis than those who were not receiving dialysis (2.6% vs. 8.0%, $P = .04$). When analyzed by type of transplant, preemptive SPK transplants (i.e., for recipients not yet receiving dialysis) had the highest incidence of thrombosis (11.4%). Nonpreemptive SPK transplants (i.e., for recipients receiving dialysis) had a 3.1% incidence of thrombosis ($P = .10$). The type of dialysis (peritoneal vs. hemodialysis) did not change this finding. Not significant for thrombosis were recipient age, body mass index, duration of diabetes, location of graft (left vs. right), or arterial reconstruction technique. Obese recipients tended to have a higher incidence of thrombosis, but this did not quite reach statistical significance.

Intraabdominal Infections

The incidence of documented intraabdominal infections decreased significantly (18.0% in era 1, 5.8% in era 2; $P = .001$). Infections were managed either by percutaneous drainage with radiologic guidance or by relaparotomy. The incidence of relaparotomy for intraabdominal infections decreased significantly (12.0% in era 2, 3.5% in era 1; P .001).

For the 213 era 2 recipients, the incidence of intraabdominal infections was slightly higher after SPK transplants (6.3%) than PAK (3.1%) or PTA (4.4%). Treatment involved graft pancreatectomy for 40% of the recipients. The others underwent drainage of abscess (percutaneously or open), débridement, and abdominal irrigation. Approximately 50% of the infections were polymicrobial; the remainder involved a single organism (*Klebsiella* 10%, *Pseudomonas* 20%, *Staphylococcus* 20%). Fungal infection was identified in only two of the era 2 recipients with polymicrobial infection. In contrast, in era 1, fungal organisms were present in 34% of intraabdominal infections.

Significant risk factors for intraabdominal infection in era 2 recipients were older donor age (older than 40 years, 16.2%; 40 years or younger, 2.9%; $P = .009$) and vascular disease in the recipient (12.3% with vs. 2.6% without, $P = .01$). Recipient obesity was associated with a significantly higher incidence of wound infections (21.8% vs. 9.5%, $P = .01$) and a trend toward a higher incidence of intraabdominal infections ($P = .10$). Not significant in this analysis were recipient age, duration of diabetes, and positive preservation fluid or donor duodenum cultures. Pretransplant dialysis

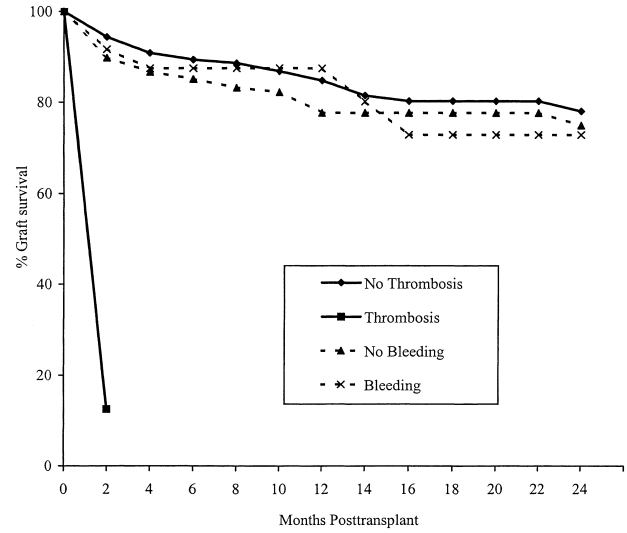

Figure 2. Graft survival rates for recipients requiring relaparotomy for bleeding and thrombosis (era 2 only).

status (preemptive vs. nonpreemptive) and type of dialysis (peritoneal vs. hemodialysis) did not influence the incidence of intraabdominal infections. Graft survival was 60% at 1 year for recipients with and 82% for those without intraabdominal infections ($P = .01$).

DISCUSSION

Pancreas transplantation is currently the only treatment of type 1 diabetes mellitus that routinely and consistently restores normoglycemia and returns long-term hemoglobin A1-C levels to normal. It has gained significant popularity during the past decade but remains significantly underused as a treatment option for the vast majority of patients with type 1 diabetes. One obvious reason is the risk of long-term immunosuppression, especially in recipients of solitary pancreas grafts who are not in renal failure and who do not need a kidney transplant. However, another major obstacle to widespread application of pancreas transplantation has been its high rate of surgical complications. In fact, it has the highest surgical complication rate of all routinely performed solid organ transplants.[8–10] Several factors contribute to this high complication rate, such as the underlying disease itself and the broad spectrum of potential pancreas graft complications (infection, necrosis, pancreatitis, fistula formation). Many centers have reported close to a 30% incidence of surgical complications,[9,10] often requiring reoperation.

At our center, during the past 5 years, we noted a significant decrease in the incidence of surgical complications. Many factors are probably responsible. In extensive analyses of our results in the 1980s and early 1990s,[5–7,11,12] we looked at the incidence of and risk factors for major surgical complications (e.g., thrombosis, intraabdominal infections, leaks, bleeding). Based on the results of those analyses, we modified our donor and recipient selection criteria, surgical techniques, and prophylaxis regimens. Also contributing to improved outcome are more effective immunosuppressive regimens, more accurate diagnosis of rejection, and more efficient but less toxic agents for treating posttransplant infections.

The division of our experience into the two eras was arbitrary, although several major changes to our protocols were made in 1994. One major change was a switch from immunosuppressive protocols based on cyclosporine and azathioprine to those based on tacrolimus and mycophenolate mofetil. Thrombosis prophylaxis using low-dose heparin and ASA was initiated on a regular basis in 1994. That same year, we added an antifungal agent (fluconazole) for the first week after the transplant as prophylaxis against fungal infections. The relaparotomy rate during the second half of era 1 (1990–1994) remained high, suggesting that these changes played some role in reducing the relaparotomy rate.

Recipient demographics did not change significantly between the two eras. SPK remained the most common of the three transplant categories, although the number of PAK transplants increased. With the current demand for cadaver kidneys and the long waiting times for SPK transplants, we find it convenient to offer a living related kidney transplant followed by a cadaver pancreas transplant to uremic diabetic patients. One notable change in demographics between the two eras was a shift toward use of younger donors. Again, this shift was based on our previous analyses, which showed older donor age to be a significant risk factor for surgical complications.[6,7,11]

The overall incidence of relaparotomy significantly decreased (32.4% in era 1 vs. 16.2% in era 2). Not only did the incidence of relaparotomy decrease, but also recipients tolerated it better in era 2. The death rate in recipients requiring relaparotomy decreased significantly (9% in era 1 vs. 4% in era 2). This decrease is probably related to improved antimicrobial therapy, more specific immunosuppressive therapy, and most importantly improved intensive care. Graft survival also improved between the two eras for recipients not requiring relaparotomy. This improvement was in part due to a higher patient survival rate, but also to a higher graft salvage rate in the current era for recipients with leaks and intraabdominal infections.

The main reason for the decrease in relaparotomy rates was the decreased incidence of vascular graft thrombosis and intraabdominal infections. Thrombosis and infections were the two most common reasons for relaparotomy in era 1. Bleeding now is the most common reason, followed by thrombosis, infections, and leaks in roughly the same incidence. SPK transplants (vs. PAK or PTA) were associated with the highest relaparotomy rate in both eras, probably reflecting the more technically involved and demanding nature of the dual-organ versus the single-organ transplant.

The most significant risk factors for relaparotomy in era 2 were older donor age and recipient obesity. In several previous analyses, we showed older donor age to be a risk factor for several surgical complications, including thrombosis and infections.[7,11] Surgical complications overall seemed to be more common in obese recipients, especially infections and thrombosis. The reason may be related to increased technical difficulties encountered in performing these procedures in obese recipients. Several reports in the kidney transplant literature show obesity to be a significant risk factor for postoperative surgical complications.[13,14]

Relaparotomy had a significant negative impact on graft survival rates. Most graft losses occurred early after the transplant and involved pancreatectomies for infarcted grafts or severe intraabdominal infections. We found no significant difference in patient survival rates for recipients requiring versus not requiring relaparotomy. This finding is in contrast to our previous era 1 report[7] demonstrating lower patient survival rates for recipients requiring versus not requiring relaparotomy. Likely reasons for the improved patient survival rates in era 2 are better critical care, better antimicrobial therapy, and performance of graft pancreatectomy early in the face of significant surgical complications.

Vascular thrombosis is the leading cause of nonimmunologic pancreas graft loss in the literature, with a reported incidence of 10% to 35%.[15–17] According to the International Pancreas Transplant Registry, thrombosis accounts for almost 60% of all nonimmunologic graft failures.[18] We noted a decline in the incidence of vascular thrombosis (10.1% in era 1, 5.6% in era 2). We believe this decline is in large part due to our prophylaxis regimen consisting of low-dose heparin and ASA. Era 1 recipients rarely underwent prophylaxis with heparin, whereas most era 2 recipients did. However, of the 213 era 2 recipients, almost 30% did not receive heparin because of bleeding or some other contraindication; the incidence of thrombosis in these recipients was 10.8% (vs. 4.0% in the 70% of recipients who received heparin).

In this analysis, older donor age was the most significant risk factor for graft thrombosis; this finding is similar to our previous report of era 1 recipients only.[11] The reason may be an increasing incidence of atherosclerotic disease in donor vessels with increasing age. Preemptive transplantation (i.e., for recipients with renal failure before they progress to dialysis) was also identified as a risk factor for thrombosis in this analysis. Recipients with advanced renal failure who are receiving dialysis have complex derangements of their coagulation system; such derangements may have a protective effect against thrombosis early after the transplant.

Prophylaxis with heparin has its own problems. The incidence of significant bleeding, as measured by the need for relaparotomy, increased in era 2, but graft survival rates were no different for recipients with versus without bleeding complications. However, vascular thrombosis always led to a graft pancreatectomy. Therefore, we continue to use heparin and ASA for prophylaxis in all recipients, because we believe that reoperation for bleeding is better than reoperation for vascular thrombosis.

Infection remains a significant concern. The immunosuppressed state, the underlying illness, and an operation involving two potentially contaminated hollow viscera (duodenum and bladder) all contribute to the risk for infection. In era 1, infection was the most common cause of relaparotomy, but the incidence significantly decreased in era 2. One reason is that current radiologic drainage techniques, using computed tomography and ultrasound guidance, allow nonoperative treatment of a greater number of intraabdominal infections. However, even if radiologically treated infections are included, the incidence of intraabdominal infections was significantly lower in era 2. Reasons probably include improved preservation of the cadaver pancreas, surgical refinements in the recipient procedure, more effective antimicrobial agents for prophylaxis, and more potent immunosuppressive regimens (e.g., tacrolimus, mycophenolate mofetil) that have decreased the acute rejection rate[19,20] and the need for bolus high-dose rejection treatment. The addition of agents such as fluconazole to our standard prophylaxis regimen has decreased the number of fungal infections. The anastomotic leak rate, unfortunately, has not changed. Because they often result in intraabdominal infections, leaks must be addressed to reduce the incidence of serious abdominal infections.

In summary, despite the limitations of a retrospective study, the results of this study, the largest single-center experience to date, demonstrate a significant decrease in the surgical risk associated with pancreas transplantation. Reasons for this decrease include identification of donor and recipient risk factors, leading to better selection criteria; improved organ-preservation techniques; refinements in surgical technique; more effective prophylaxis regimens; and improved immunosuppressive regimens. Widespread application of pancreas transplantation has been limited in part by its high surgical complication rate. Our present documentation of decreased surgical complications supports our contention that more widespread application is warranted, especially for PTA and PAK transplants. A surgical cure for diabetes is now a viable option.

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