

Low Rates of Short- and Long-term Graft Loss After Kidney-Pancreas Transplant From a Single Center

Denise S. Tai, MD; Johnny Hong, MD; Ronald W. Busuttil, MD, PhD; Gerald S. Lipshutz, MD, MS

Importance: Since the 1980s, pancreas transplant has become the most effective treatment strategy to restore euglycemia in patients with type 1 diabetes mellitus. However, technical complications and BK virus nephropathy continue to be important causes of early and late graft loss. These and other complications lead to cited 1- and 3-year graft survival rates of 74% and 67% (pancreas) and 81% and 73% (kidney).

Objective: To examine our center's outcomes with pancreas-kidney transplant and early BK virus screening and treatment.

Design: Prospective study from August 2004 to January 2012.

Setting: University medical center.

Participants: Sixty-five patients with type 1 diabetes who underwent simultaneous kidney and pancreas, pancreas after kidney, or pancreas transplant alone at a single center.

Intervention: Pancreas transplant.

Main Outcome Measures: Pancreas and kidney survival; patient survival; and kidney loss due to BK virus nephropathy.

Results: Patient survival at 1, 3, and 5 years was 100%, 98.4%, and 98.4%, respectively. Of 2 early pancreatic allograft losses, 1 was due to thrombosis (1.6%). One- and 5-year pancreas graft survival rates were 95.4% and 92.3%; losses after more than 1 year were due to rejection. Kidney survival rates were 100% and 95.2% at 1 and 5 years; losses were due to nephropathy and noncompliance, with 1 death with function. BK virus incidence was 29.2%, with no graft losses due to BK infection.

Conclusions and Relevance: While pancreas transplant can be complicated by early graft loss, our results suggest that excellent outcomes at 5 years can be achieved. Posttransplant BK virus screening and treatment are essential tools to long-term success.

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DIABETES MELLITUS IS A chronic disease with both profound individual and socioeconomic burden. In 2007, the US health care costs attributed to diabetes exceeded \$174 billion, an estimate expected to escalate with the increased longevity and growing prevalence in elderly and pediatric obese populations, respectively.^{1,2} More importantly, the deleterious effects of diabetes on individual health lead to an incalculable decline in quality of life via progressive multisystem complications. For patients with type 1 diabetes mellitus (T1DM), the benefits of intensive blood glucose control in delaying diabetic nephropathy, retinopathy, and neuropathy have been well established since the seminal Diabetes Control and Complications Trial.³ Yet despite advances in the pharmacologic management of T1DM, safe and physiologic ex-

ogenous insulin delivery remains difficult to achieve for many patients.

Pancreas transplant is a highly effective treatment strategy to restore long-term euglycemia and stabilize the multi-organ derangements caused by T1DM.⁴ The significantly improved quality of life, freedom from exogenous insulin, relief of life-threatening hypoglycemic episodes, and potential survival benefit have furthered transplant as an acceptable therapeutic option over the past 2 decades, albeit at the expense of lifelong immunosuppression.⁵ Accordingly, pancreas transplants are typically performed in patients with T1DM with end-stage renal disease requiring kidney transplant, thus obligating the use of immunosuppression. The timing of pancreas transplant is either simultaneous with kidney transplant (SPK), after kidney transplant (PAK), or performed alone (PTA), with operative decision making dependent on pa-

Author Affiliations:
Department of Surgery, David Geffen School of Medicine at University of California, Los Angeles.

tient risk factors, kidney function, and organ donor availability.

In 1966, William Kelly performed the first simultaneous pancreas and kidney transplant at the University of Minnesota.⁶ Although technical refinement has improved the rate of surgical complications and graft failure since the 1980s, pancreas transplant is still associated with significantly higher rates of perioperative morbidity (estimated to be as high as 10%-15%) than other solid organ transplants.^{5,7} Early postoperative complications recognized to confer increased risk of graft loss include graft thrombosis, hemorrhage, pancreatitis, and enteric intestinal leak. In addition, recipient factors such as tobacco use, obesity, and cardiovascular and cerebrovascular disease compound the overall risk.

Importantly, polyomavirus-associated nephropathy, also known as BK virus nephropathy (BKVN), is well recognized as an important cause of kidney allograft dysfunction and loss in solitary renal transplant and kidney-pancreas transplant recipients (although it has not been reported to cause pancreas allograft dysfunction).⁸⁻¹¹ Once BK virus is diagnosed, kidney graft loss has been reported to be as high as 45% at 6 months.^{12,13} In a prior study by Lipshutz et al,¹⁴ the rate of BKVN in SPK patients at a single center was found to be 6.6%. A similar report in the literature determined their institutional rate at 7.5%.^{12,15} With no reliably effective antiviral agents available, the treatment of BK virus infection and nephropathy remains poorly defined.¹⁶ Currently, the primary mode of intervention is reduction of maintenance immunosuppression. However, both protocols and success rates remain heterogeneous and require further study in SPK patients.¹⁶⁻¹⁹

The purpose of the present study was to (1) report our short- and long-term results of allograft and patient survival of kidney-pancreas allograft recipients; 2) define the causes for allograft loss, both short and long term; and 3) report the incidence of BK virus infection in kidney-pancreas transplant recipients and prospectively determine the influence of immunosuppression withdrawal on the survival of both the kidney and pancreas allografts.

METHODS

PATIENTS AND DATA COLLECTION

This study was approved by the Committee for Human Research at the University of California, Los Angeles (UCLA) (institutional review board 11-003148). All pancreas transplant operations (SPK, PAK, and PTA) and patients at UCLA from August 2004 to January 2012 were followed up to collect recipient, transplant, and posttransplant data.

PRETRANSPLANT AND POSTTRANSPLANT CARDIOVASCULAR SCREENING

All patients from August 2004 to January 2012 were evaluated by a UCLA transplant cardiologist and underwent preoperative cardiac stress testing. Further testing was performed for higher-risk candidates including those older than 45 years with 25 years of insulin dependence and smoking or cardiac his-

tory. After activation on the transplant list, pretransplant patients underwent repeated cardiac stress testing yearly until transplant.

KIDNEY AND PANCREAS TRANSPLANT PROCEDURES

Donor pancreata and kidneys were procured from young deceased donors without evidence of pancreatic or renal dysfunction. Donor selection, operative technique, and postoperative management were performed as previously described by Schnickel et al.²⁰

After discharge, patients were followed up closely as outpatients. Urine and blood screening were performed for BK virus routinely posttransplant and if detected, monthly laboratory evaluation was performed until resolution of viremia/viruria. Routine screening was also performed for cytomegalovirus and urinary tract infections.

IMMUNOSUPPRESSION AND TREATMENT OF REJECTION

Immunosuppression consisted of induction with antithymocyte globulin and methylprednisolone and maintenance with tacrolimus, mycophenolate mofetil, and prednisone.²⁰ Tacrolimus, a calcineurin inhibitor, was initiated on postoperative day 2 unless there was evidence of delayed kidney allograft function. Tacrolimus levels of 12 to 14 ng/mL were maintained for the first 6 months, then 10 ng/mL from months 7 to 12, and 7 to 9 ng/mL thereafter. In patients where BK viremia/viruria was detected, levels as low as 5 ng/mL were tolerated. Mycophenolate mofetil was started on postoperative day 6 at 500 mg twice a day and increased to 750 mg twice a day on the subsequent day. After completion of thymoglobulin induction, patients began prednisone tapering from 20 to 5 mg daily over the first month. For patients exhibiting mild hyperglycemia, tacrolimus was changed to cyclosporine (n=3), with levels of 200 to 300 ng/mL for the first year and 100 to 200 ng/mL thereafter.

Renal and pancreas allograft function were monitored by levels of creatinine and blood glucose and amylase and lipase, respectively. Renal allograft biopsy was performed if creatinine was elevated 20% or more above baseline and pancreas biopsy was performed for unexplained amylase or lipase elevations and/or hyperglycemia. All rejection episodes were diagnosed by biopsy and treated with thymoglobulin and steroid taper. Patients who had an episode of rejection were never completely weaned from prednisone.

BK VIRUS SCREENING AND IMMUNOSUPPRESSION WITHDRAWAL

Screening for BK virus in urine and blood was performed by quantitative polymerase chain reaction assay. A lower limit of detection in urine was less than 5 copies/mL and blood was 625 copies/mL with a linear range of 625 to 6.25×10^9 copies/mL. If BK virus was detected, mycophenolate mofetil was withdrawn typically over 3 months with close surveillance of serum creatinine, amylase, and lipase levels.

STATISTICS

Multivariate logistic regression analysis to assess for independent predictors of BK virus was performed using SPSS version 19 (IBM SPSS).

Table. Renal and Pancreas Transplant Donor Demographics

Demographic	Value
Pancreas donor age, y, mean (SD) [range]	21.5 (5.2) [15-39]
Pancreas donor cause of brain death, No.	
GSW	22
MVC/MCC/PVC head injury	22
Anoxia	8
Aneurysm/ICH	5
Other CHI	8
Cold ischemia time, h, mean (SD) [range]	
Kidney	6.42 (1.36) [4.44-14.04]
Pancreas	8.43 (1.37) [5.09-14.54]
Sex, No. (%)	
M	49 (75.4)
F	16 (24.6)
BMI, mean (SD)	23.8 (2.9)
Race (not recorded, n=6), No.	
White	23
African American	5
Hispanic	29
Other	2
Renal donor type, No.	
Donation after brain death	54
Donation after cardiac death	0
Living, related	8
Living, unrelated	3

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHI, closed head injury; GSW, gunshot wound; ICH, intracerebral hemorrhage; MCC, motorcycle crash; MVC, motor vehicle crash; PVC, pedestrian-vehicle crash.

INFECTION AND THROMBOSIS PROPHYLAXIS

Routine infection prophylaxis was as follows: (1) *Pneumocystis carinii* pneumonia (PCP) prophylaxis: combined trimethoprim and sulfamethoxazole (Septra double strength) 4 times a day for 3 months (changed programwide to 12 months in 2010 after PCP outbreak); (2) fungal prophylaxis: fluconazole, 400 mg daily for 2 months; and (3) cytomegalovirus prophylaxis: valganciclovir hydrochloride, 900 mg daily for 3 to 6 months depending on risk profile.²⁰ Selection of thrombosis prophylaxis was dependent on whether the transplant was an SPK, PAK, or PTA, as previously described.²⁰

RESULTS

DEMOGRAPHICS AND PATIENT SURVIVAL

From August 2004 to January 2012, 65 patients with T1DM underwent pancreas transplant (50.7% female; mean [SD] age, 42.8 [7.5] years; mean [SD] body mass index, 26.0 [3.5] [calculated as weight in kilograms divided by height in meters squared]) and were prospectively followed up after undergoing SPK (n=45), PAK (n=19), or PTA (n=1) transplant (**Table**).

Mean (SD) follow-up was 1454 (728) days. Thirty-day and 1-year patient survival rates were 100%. Three-year, 5-year, and 7-year patient survival was 98.5% (**Figure**). In this series of 65 patients, there was only 1 death. The cause is unknown because the patient was lost to follow-up 2 years after PAK. Two patients developed

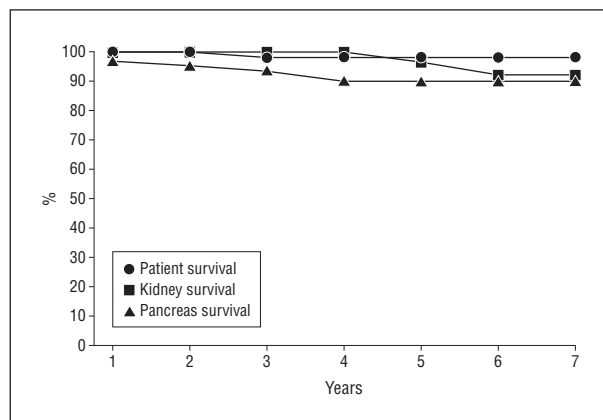


Figure. Patient survival and failure-free survival of kidney and pancreas allografts after transplant.

severe PCP necessitating prolonged hospitalizations. One patient (male, Hispanic, developed PCP 2 years and 8 months after SPK) recovered and has maintained normal pancreatic and kidney allograft function. A second patient (male, African American, developed PCP 5 years after SPK) was treated with intravenous pentamidine isethionate because of a national shortage of intravenous trimethoprim/sulfamethoxazole at the time. Because of the toxicity of pentamidine to islets,²¹⁻²³ the patient has continued to require long-acting insulin. Both patients are alive and active adults at this time.

KIDNEY ALLOGRAFT SURVIVAL AND INCIDENCE OF BK VIRUS INFECTION

Overall kidney allograft survival was 96.9% (2 losses) with a third censored for death with function. One-, 3-, and 5-year kidney allograft survival rates were 100% and 7-year survival was 98.5% (**Figure**). Both kidneys were lost in PAK recipients. One kidney (and pancreas) allograft lost function 4 years and 9 months after PAK (5 years and 8 months after kidney transplant) because of noncompliance with medications and development of cellular and humoral rejection. The second kidney was lost because of calcineurin inhibitor toxicity and chronic allograft nephropathy 5 years and 6 months after PAK (9 years after kidney transplant).

BK viremia was diagnosed in 29.2% (n = 19) of recipients. Three of these patients were the recipient of a PAK and 16 were recipients of an SPK; the single PTA recipient has not demonstrated BK viremia. BK viremia was diagnosed a mean (SD) 485 (378) days (range, 90-1465 days) after receiving a pancreas transplant. BK viremia was detected in 12.3% (n = 8) of recipients, all of whom had been previously diagnosed with BK viremia. One of these patients was a PAK recipient and 7 were recipients of an SPK. BK viremia was diagnosed a mean (SD) 482 (318) days (range, 86-947 days) after receiving a pancreas transplant. Neither of the patients who lost kidneys in this series (n = 2) demonstrated BK viremia or BK viremia.

Patients with BK were treated by weaning mycophenolate mofetil to 250 mg orally twice a day followed by discontinuation. No patients developed rejection dur-

ing the process or subsequently. Five of the 8 patients (62.5%) had resolution of BK viremia and 8 of the 19 patients (40%) had resolution of BK viruria. All patients with persistent BK viremia/viruria have had a progressive decline in viral titer since withdrawal of mycophenolate mofetil. Lowering the tacrolimus level in these patients has led to further declines in viral load.

A multivariate logistic regression analysis was performed to assess for independent predictors of BK virus. Variables included recipient age, ethnicity, and sex; donor sex, blood type, and race; type of transplant (SPK vs PAK vs PTA); and year of transplant. There were no variables that independently predicted BK virus in this regression analysis. Known risk factors (ie, ureteral stent and diabetes mellitus) were excluded because all patients had a history of diabetes mellitus and had a stent at the time of transplant.^{24,25}

PANCREAS ALLOGRAFT SURVIVAL

Overall pancreas allograft survival was 92.3% (5 losses). All losses occurred in PAK recipients. Thirty-day and 1-year allograft survival rates were 96.9% and 95.4%, respectively, while 3-year survival was 93.8% (Figure). Five- and 7-year pancreas allograft survival rates were 92.3%. One graft was lost in the first week posttransplant because of allograft thrombosis. Notably, no grafts were lost from duodenal leaks or primary nonfunction. Furthermore, no pancreatic allograft rejection developed during selected withdrawal of immunosuppression for BK viruria/viremia.

DISCUSSION

Over the past 50 years, pancreas transplant has evolved from an experimental procedure to a highly successful therapeutic option for patients with T1DM with end-stage renal disease. Improved surgical technique and more effective immunosuppression have been key to the improved rates of graft survival and mortality. However, unlike with other solid organ transplants, pancreas transplant continues to experience significant technical complications, with limited evidence-based medicine to help guide definitive technique.²⁶ Specifically, management of exocrine and endocrine drainage is a challenge unique to pancreas transplant. Devastating complications from early methods of exocrine drainage (pancreatic duct ligation, injections with polymers) prompted exploration of different approaches, most notably donor duodenum to bladder drainage initiated in the 1980s. Today, the most popular method involves enteric drainage with donor duodenum to jejunum, although other methods such as duodenum to ileum, gastric antrum, or Roux-en-Y are still practiced.^{5,27} Portal vs systemic endocrine drainage of insulin has also been a subject of controversy. Early evidence suggested that physiologic portal venous drainage and the preservation of liver first pass effect may improve graft survival and avoid potential cardiovascular complications from systemic insulin release.^{26,28} Recent data, however, suggest there may be little difference in outcomes between either group.²⁹

These challenges inherent to pancreas transplant have portended the technical complications that remain problematic for graft survival in the first year. Between 1994 and 2003, the University of Minnesota reported their technical pancreatic graft loss at 13.1% in a series of more than 900 transplants.¹⁵ Among the causes were graft thrombosis, pancreatitis, leak, and bleeding. Our study is one of the few to report both short- and long-term outcomes and causes of allograft loss. From 2004 to 2012, our patient survival rates at 1, 3, and 5 years were 100%, 98.4%, and 98.4%, respectively. To date, our kidney allograft survival is 97% (2 losses) and pancreas allograft survival is 92.3% (5 losses). Only 1 pancreas graft was lost in the immediate perioperative period from thrombosis; 2 were lost from infection and 2 from noncompliance. No grafts were lost from leak or primary nonfunction. From 2010, the United Network for Organ Sharing reports 1-, 3-, and 5-year patient survival rates of 94.7%, 90.7%, and 86.5%, respectively. Kidney and pancreas graft survival rates at 1, 3, and 5 years were 92.2%, 84.7%, and 77.7% and 84.5%, 77.9%, and 71.3%, respectively.³⁰

In this series, we have shown that excellent short- and long-term results can be produced despite being a relatively low-volume center. We believe this is due to a single experienced surgeon performing all cases and careful postoperative monitoring. Although an inverse association between hospital procedure volume and postoperative patient outcome has been demonstrated for some adult and pediatric solid organ transplant procedures, this has not been studied for pancreas transplant.²¹⁻²³ Specifically, our study (average of 9-10 pancreas transplants per year) does not demonstrate such a volume effect. Notably, all lost pancreas allografts occurred in PAK recipients, which is mirrored by national data, reflecting that pancreatic graft function is considerably shorter in PAK than SPK recipients.⁴ Despite these risks, we believe PAK in a selected population can still confer benefit from glycemic control.

BK virus nephropathy has been well studied in the single-kidney transplant population but there remains a paucity of data on the effects of BKVN and immunosuppression reduction in SPK and PAK recipients. It is known that asymptomatic BK viruria normally precedes viremia and subsequent active nephropathy. Detection of the BK virus prior to the development of BKVN presents an opportunity for preemptive treatment with early immunosuppression reduction. To our knowledge, this is the first prospective study on BK viruria/viremia screening and early immunosuppression reduction in SPK and PAK recipients, with outcomes measured by long-term graft survival and resolution of BK viruria/viremia. Several retrospective case series have shown institutional rates of BKVN in SPK patients to range from 2.9% to 6.2%, with subsequent kidney allograft loss between 0% and 89%.³¹ The retrospective review by Lipshutz et al¹⁴ of 146 SPK recipients from 1996 to 2002 identified a BKVN incidence of 6.6%, more than half of whom subsequently had kidney allograft loss. Notably, no pancreas grafts were reported to be lost from BKVN in any of these case series.

In 2004, we established a program for routine BK virus screening and early initiation of mycophenolate mofetil

withdrawal in all SPK and PAK recipients. Our results have shown a 0% incidence of BKVN and, subsequently, no kidney losses from BKVN. Furthermore, 62.5% and 40% of recipients who developed BK viremia and viruria, respectively, experienced resolution after treatment. These findings suggest that routine screening and early treatment of BK virus in SPK and PAK recipients can be a powerful tool to help prevent the potential development of BKVN and its devastating sequelae including kidney graft dysfunction, loss, or ureteral strictures.

Interestingly, our results showed a fairly high incidence of BK virus detection; 29.2% of patients were found to have viruria. Given that 80% to 90% of the population was seropositive for polyomavirus, this could represent the natural history of BK virus reactivation in the immunosuppressed population. Furthermore, while quantitative polymerase chain reaction is largely the tool used to detect BK viral DNA, other methods such as urine cytology and urine VPI messenger RNA have also been used, which could attribute to variance in detected cases among institutions.³² A multivariate logistic regression analysis was performed and there were no independent risk factors that predicted for BK virus in our series. Also unexplained is the 5 times higher rate of BK virus detected in SPK vs PAK recipients. These results appear paradoxical in that PAK recipients at our institution receive a second course of antithymocyte induction and have higher levels of tacrolimus maintained long term. The reason for a predominance of these cases in SPK compared with PAK recipients remains unclear.

There are limitations to this study including its involvement with only a single center. Furthermore, the exclusion of recipients older than 55 years potentially avoids a subpopulation of patients with comorbid conditions that may lead to worse overall outcomes. Several possible explanations also exist for our high patient and graft survival. First, the majority of donors were young with low body mass index. Second, we meticulously perform the back table preparation to avoid bleeding during reperfusion and we consistently perform a 2-layered hand-sewn intestinal anastomosis, which to date has not led to an anastomotic leak. Third, all planned recipients are seen by our team cardiologist pretransplant and undergo necessary angiography prior to transplant. To date, there have been no postoperative myocardial infarctions in our recipient population. Finally, all recipients are followed up lifelong by 1 transplant surgeon, with careful BK surveillance and immunosuppression adjustment. We credit this close outpatient follow-up to achievement of the long-term outcomes obtained and prevention of kidney allograft loss by BKVN.

Our results show that pancreas transplant is a highly effective option for patients with T1DM with end-stage renal disease and can be performed safely with excellent outcomes. Screening for BK virus with early treatment in kidney-pancreas transplant recipients are important tools to help prevent BKVN and subsequent kidney graft loss and dysfunction. Future multicenter prospective trials will be valuable to determine the durability of these measures.

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Correspondence: Gerald S. Lipshutz, MD, MS, Department of Surgery, David Geffen School of Medicine at UCLA, 77-120 CHS, Los Angeles, CA 90095-7054 (glipshutz@mednet.ucla.edu).

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