CHAPTER 73

Pancreatic Transplantation

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INTRODUCTION

The treatment options for insulin-dependent diabetes mellitus are either exogenous insulin administration or β-cell replacement by pancreas or islet transplantation. Exogenous insulin administration is burdensome to the patient and gives imperfect glycemic control, predisposing to secondary complications of the eyes, nerves, kidneys, and other systems. On the other hand, β-cell replacement, when successful, establishes a constant euglycemic state but requires major surgery (a pancreas transplant) and immunosuppression to prevent rejection, predisposing to complications, often compounded by comorbidities from pre-existing diabetes.

The Diabetes Control and Complications Trial (1) showed that intensive insulin therapy (multiple injections per day with dose adjusted by frequent blood sugar determinations) decreased (although rarely normalized) glycosylated hemoglobin (HgbA1c) levels and reduced the rate of secondary complications (2). The threshold for totally eliminating the risks of secondary diabetic complications is perfect glycemic control, an objective that can be achieved by the most sophisticated exogenous insulin delivery devices unfortunately at the cost of frequent hypoglycemic episodes. This may change in the future with real-time glucose monitoring systems combined with insulin pumps (3,4). Pancreas transplantation induces insulin independence in diabetic recipients without the risk of hypoglycemia and can ameliorate secondary complications. With major advances in the management of pancreas transplantation, the success rate of pancreas transplants has progressively increased during the past two decades (5,6). Today’s recipients have a high probability of being insulin independent for years, if not indefinitely.

Historically, islet transplants have been less successful for a variety of reasons. In the late 1990s at the University of Alberta, insulin independence was achieved in several consecutive recipients by sequential grafting of islets from multiple donors and the use of a steroid-free nondiabeticogenic immunosuppressive regimen (7). In another series from the University of Minnesota with a similar regimen, single-donor islet transplants induced insulin independence (8). In the Minnesota series, the donors had a high body mass index and the recipients had a low body mass index. Thus, the net number of islets transplanted per unit weight was similar in the Alberta and Minnesota series. Islet transplants can succeed with stringent donor and recipient selections, but is yet not able to supersede pancreas transplants as the mainstay of β-cell replacement. Until islet transplants can consistently succeed from a single donor, regardless of size or recipient insulin requirements, an integrated approach is preferable (9): low-risk patients should undergo a surgically more challenging pancreas transplant, high-risk patients an islet transplant.

Although short-term islet graft survival appears promising (even with single donors) (10), long-term graft function after islet transplants (even with multiple donors) continues to be a major impediment to rapid progress. In the University of Alberta series, only 10% of islet transplant recipients were insulin independent at 5 years posttransplant (11).

The main tradeoff for recipients of β-cell allografts is the need for immunosuppression. A successful graft makes the recipient euglycemic and normalizes HgbA1c levels (11,12), but the combined risks of immunosuppression and pancreas transplant surgery must be weighed against the long-term risks of imperfect glycemic control and of development of secondary complications with exogenous insulin. A randomized prospective trial has not been done to weigh these risks. The burden of day-to-day management of diabetes, with need for multiple needlesticks to inject insulin and monitor blood sugar levels tilts the balance in favor of a transplant for many diabetic patients. Furthermore, antirejection strategies are continually being developed to decrease the side effects of immunosuppression. Nevertheless, only a few institutions perform pancreas transplants soon after the onset of the disease (13).

The main indications for a pancreas transplant in patients with normal kidney function have been labile diabetes with frequent insulin reactions and hypoglycemic unawareness, a syndrome that may emerge years after the onset of diabetes, particularly in patients with autonomic neuropathy (14). However, even for nonlabile diabetic patients who attempt tight control by intensive glucose monitoring, literature shows a high rate of secondary complications that are just as morbid as (15), if not more so than, chronic immunosuppressive complications in organ allograft recipients (16,17). Thus, for a patient who wishes to avoid a lifetime of insulin injections and glucose monitoring and who prefers the risks of immunosuppressive complications to the secondary complications of diabetes, a pancreas transplant can be performed with good results (18). This also applies to type 2 diabetics who are obligatory insulin dependent. About 5% of pancreas transplants are performed in selected type 2 diabetics (19).

In the past, most pancreas transplant candidates had advanced diabetic nephropathy and required a kidney transplant also. As the risks of immunosuppression are assumed because of the kidney transplant, a simultaneous or sequential pancreas transplant does not pose any additional risks other than surgery (13). Indeed, pancreas transplants have been done in renal allograft recipients who meet the criteria for type 2 diabetes with elimination of the need for exogenous insulin (20).

RECIPIENT CATEGORIES

Diabetic pancreas transplant candidates are divided into three categories: uremic (need a kidney transplant), posturemic (have a functioning kidney transplant), and nonuremic (do not need a kidney transplant). For candidates who are uremic, the options
are to receive kidney and pancreas transplants either simultaneously in one operation or sequentially in separate operations. The decision as to which option to take is usually based on the availability and suitability of living and cadaveric donors for one or both organs. Accordingly, there are three broad categories of recipients: simultaneous pancreas–kidney (SPK), pancreas after kidney (PAK), and pancreas transplants alone (PTA).

PK Transplants
Most SPK transplants have been done with both organs coming from the same cadaveric donor. Because a large number of patients are waiting for a kidney, unless priority is given to SPK candidates, waiting times tend to be long (years). Thus, to avoid two operations and a long wait, a simultaneous kidney and segmental pancreas transplant from a living donor can be done (20–22). Only a few centers offer this option (23,24). There has been a report from Japan of a successful islet transplantation from a live donor (25). Therefore, a simultaneous living-donor islet kidney transplant may become a viable option in the future (26,27). If a living donor is suitable for or only willing to give a kidney, another option is a simultaneous living-donor kidney and cadaveric pancreas transplant (23,24). For these options, the living donor kidney usually must be available on a moment’s notice (the same as for the recipient), as the cadaveric pancreas must be transplanted soon after procurement. Alternatively, a recipient of a scheduled living-donor kidney transplant could also receive a cadaveric pancreas simultaneously if one became available fortuitously. If not, and only a kidney is transplanted, the recipient becomes a PAK candidate.

PAK Transplants
For nephropathic diabetic patients who have already undergone a kidney transplant from a living or a cadaveric donor, a PAK transplant can be performed. Most PAK transplants today are done in patients who previously received a living-donor kidney because suitable uremic diabetic patients without a living donor will undergo a cadaveric pancreas transplant. Although a PAK means a uremic diabetic patient requires a living donor will undergo a cadaveric pancreas transplant. The interval between the living-donor kidney and cadaveric pancreas transplant depends on several factors, including recipient recovery from the kidney transplant and donor availability, but the outcome is similar for all intervals more than 1 month. PAK is the largest pancreas transplant category at the University of Minnesota (28,29).

PTA Transplants
For recipients with adequate kidney function, a solitary pancreas transplant can be performed from either a living or a cadaveric donor. Because the waiting time for a cadaveric pancreas is relatively short at the present time, living-donor pancreas transplants are done infrequently, but are particularly indicated if a candidate has a high panel-reactive antibody and a negative cross-match to a living donor. Most PTA candidates have problems with glycemic control, hypoglycemic unawareness, and frequent insulin reactions. A successful PTA not only obviates these problems, but also improves the quality of life, and may ameliorate secondary complications, thus increasing the applicability of PTA (28–30).

EVOLUTION AND IMPROVEMENTS
The first clinical pancreas transplant was performed at the University of Minnesota in 1966 (31). The number of transplants remained low during the 1970s, but progressively increased in the 1980s, following the introduction of cyclosporine. By the end of 2014, almost 50,000 pancreas transplants had been performed in 55 countries around the world (Fig. 73.1), including almost 30,000 in the United States (Fig. 73.2) (6).

The history of pancreas transplants involves many different techniques and eras (32). The first series of pancreas transplants at the University of Minnesota used enteric drainage (ED) (32). Urinary drainage was first done into the ureter by Gliedman in the early 1970s (33,34), then via duct injection by Dubernard et al. (35) in 1974, and then via direct bladder drainage (BD) by Sollinger et al. (36) in 1982. During the 1980s, BD became the predominant technique (Fig. 73.3) with good results (37). ED was still used (38), although sparingly, but since the late 1990s it has become the most frequent technique, especially in SPK transplants.

Venous drainage of the pancreas has also evolved over the years. Portal drainage was used with segmental grafts in the 1980s (32,39–42). For whole-organ pancreas transplants, systemic drainage was the norm until the 1990s, when portal drainage gained popularity, especially with ED (43,44), as opposed to BD (45). Between 1996 and 2000, about one-fifth of all SPKs used portal drainage, by anastomosis either to the recipient splenic vein (40) or, more commonly, to the superior mesenteric vein (Fig. 73.5) (46). Over the past decade, systemic drainage has reestablished itself as the most common technique (5,6).

Before techniques were developed to procure both liver and pancreas grafts with intact blood supply (47,48), segmental pancreas grafts were commonly used. Since the early 1990s, whole-organ pancreaticoduodenal grafts predominate (49), although segmental grafts are still used for living-donor pancreas transplants (28). The first living-donor pancreas transplant was performed at the University of Minnesota in 1979 (50). The early series of living-donor pancreas transplants consisted of solitary pancreases because the rejection rate of cadaveric pancreases was high (23). In the 1990s, living-donor pancreas transplants were predominantly performed in combination with a kidney from the same donor (Fig. 73.6) (22,51–53). Living-donor segmental pancreatectomy are now performed laparoscopically (54). Another approach, as previously mentioned, is to perform a living-donor kidney transplant simultaneously with a cadaveric pancreas transplant (24).

Immunosuppressive regimens have made great strides over the years. Today, there are more than 100 pancreas transplant centers in the United States (55). Some centers have reported extensive experience. For example, more than 1,000 SPK transplants have been performed at the University of Wisconsin (UW) (56), and more than 2,000 pancreas transplants of all categories have been performed at the University of Minnesota (28). The International Pancreas Transplant Registry, formed in 1980, collects data from all centers in the world (57) and is the best resource for outcome analysis.
Outcomes after pancreas transplants have consistently improved over the years (5,6). The latest report from the International Pancreas Transplant Registry (6) outlined recent results, focusing on U.S. transplants from 2009 through 2013, including more than 3,900 SPK, more than 500 PAK, and 389 PTA cases. Patient survival rates for all three categories was more than 95% at 1 year posttransplant (Fig. 73.7). Primary pancreas graft survival rates at 1 year posttransplant were higher for SPK (88.9%) than for PAK (84.4%) and PTA (81.5%) recipients (Fig. 73.8). Graft loss from rejection was low at 1 year in all three categories (1.7% SPK, 4.4% PAK, 5.5% PTA). In the majority of all transplants, ED was used for duct management, and of the ED transplants, portal venous drainage was used in about 20% of SPK and 10% of solitary transplants. Although overall graft function did not vary with ED or BD, the PTA group had a higher immunologic graft loss rate in ED versus BD cases. BD may result in earlier diagnosis of rejection because of the ability to monitor for a decline in urine amylase activity as a marker (28). Nevertheless, the late rejection rate is higher in the PTA than in other categories.
who have developed secondary complications of diabetes. The progression of complications is halted by a functioning pancreas graft. In fact, even an improvement in neuropathy has been documented (5,22,34,59,60). In addition to improvement in glomerular architecture, a recent study shows that interstitial expansion is reversible, and atrophic tubules can be reabsorbed (61). Advanced retinopathy and vascular disease, however, are unaffected (62). Atherosclerotic risk factors decrease and endothelial function improves posttransplant (63). A pancreas transplant should be offered early, before the onset of complications of diabetes, to interested patients.

**INDICATIONS AND CONTRAINDICATIONS**

The indications for a pancreas transplant have evolved and expanded over the years as the results have improved. The position statement of the American Diabetes Association (58) on indications for a pancreas transplant (Table 73.1) is conservative. A pancreas transplant is also indicated for patients who have developed secondary complications of diabetes. The progression of complications is halted by a functioning pancreas graft. In fact, even an improvement in neuropathy has been documented (5,22,34,59,60). In addition to improvement in glomerular architecture, a recent study shows that interstitial expansion is reversible, and atrophic tubules can be reabsorbed (61). Advanced retinopathy and vascular disease, however, are unaffected (62). Atherosclerotic risk factors decrease and endothelial function improves posttransplant (63). A pancreas transplant should be offered early, before the onset of complications of diabetes, to interested patients.
who understand the risk of immunosuppression versus the benefit of insulin independence and freedom from diabetic complications.

Contraindications include those for any other transplant, such as malignancy, active infections, noncompliance, serious psychosocial problems, and prohibitive cardiovascular risk. Candidates with advanced vascular disease have an increased risk of surgical complications, yet those who do well post-transplant greatly benefit from stabilization of their cardiovascular risk.

Although it was clear that insulin-dependent recipients with renal failure benefited from a pancreas transplant in addition to the kidney, the survival benefit for pancreas transplant in patients with preserved renal function was questioned by at least one study (64). However, a more comprehensive reanalysis revealed that there was no increased mortality for solitary pancreas transplant recipients over wait-listed patients (65,66).

**FIGURE 73.6** Simultaneous segmental pancreas and kidney transplant from a living donor (LD). Either bladder drainage (BD) or enteric drainage (ED) can be used, but the BD technique has a lower complication rate and is illustrated.

**FIGURE 73.7** Patient survival after primary deceased donor pancreas transplants in the United States from 1980 to 2013 by the International Pancreas Transplant Registry. PAK, pancreas after kidney; PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney.

**FIGURE 73.8** Pancreas graft survival after primary deceased donor pancreas transplants in the United States from 1980 to 2013 by International Pancreas Transplant Registry. PAK, pancreas after kidney; PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney.
because bladder dysfunction predisposes to graft pancreatitis. A prokinetic agent may be indicated to treat gastroparesis. A pressive medications may worsen gastrointestinal dysfunction. done to rule out autonomic dysfunction. Some immunosup-
tion (72). Abnormal liver function tests or the diagnosis of viral hepatitis should be followed up with a liver biopsy to rule out viral hepatitis (either B or C). dobutamine stress echocardiograms are used for cardiac evaluation with good results (70). Once significant CAD is detected, aggressive treatment by revascular-
ization, angioplasty, or stenting is recommended. In one study, revascularized transplant candidates had significantly fewer postoperative cardiac events, as compared with those who received medical therapy alone (71).

A detailed vascular examination must be done to rule out significant vascular insufficiency. If such insufficiency is found, it may need correction pretransplant because the transplant surgery, involving an anastomosis to the iliac artery, may fur-
ther diminish lower-extremity blood flow. Pulmonary function tests are indicated in chronic smokers and patients with a history of chronic pulmonary disease. Postoperative intensive care unit monitoring and perioperative bronchodilator therapy may be indicated in some patients. Liver function tests should be done to rule out hepatic insufficiency and viral hepatitis. The diagnosis of viral hepatitis (either B or C) is associated with worse long-term outcome after extrahepatic transplantation (72). Abnormal liver function tests or the diagnosis of viral hepatitis should be followed up with a liver biopsy to rule out cirrhosis. The presence of cirrhosis is a contraindication for pancreas transplant. A gastrointestinal evaluation must be done to rule out autonomic dysfunction. Some immunosup-
pressive medications may worsen gastrointestinal dysfunction. A prokinetic agent may be indicated to treat gastroparesis. A urologic examination is especially important for BD recipients because bladder dysfunction predisposes to graft pancreatitis.

**PRETRANSPLANT EVALUATION**

The pretransplant workup should include a detailed medical and psychosocial evaluation. Cardiac risk assessment is mandatory because diabetes is a major risk factor for coronary artery disease (CAD). Cardiologists vary on the type of test to screen for CAD in pretransplant diabetic patients. Coronary angiograms are performed in most candidates. Noninvasive tests are not very sensitive for CAD and poorly predictive for subsequent postoperative events in long-standing diabetic patients (67,68). With the use of iso-osmolar radio contrast, there does not seem to be an increased risk of contrast-induced nephropathy in patients with chronic kidney disease (69). In selected patients (i.e., young, healthy patients with short-duration diabetes), dobutamine stress echocardiograms are used for cardiac evaluation with good results (70). Once significant CAD is detected, aggressive treatment by revascular-
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**DECEASED DONOR SELECTION**

Pancreas donor selection criteria are not standardized, but instead vary from center to center. Absolute contraindica-
tions are the obvious ones applied to most solid organs: active hepatitis B, C, and non A–non B; human immunodeficiency virus; non–central nervous system (CNS) malignancy; surgical or traumatic damage to the pancreas; history of diabetes mellitus; pancreatitis; and extremes of age (younger than 10 or older than 60 years). Prolonged intensive care unit stay and duration of brain death have been associated with an increased risk of graft failure (73). Other studies have shown that donor age is important; even middle-aged donors (older than 40 years) are associated with increased complications and graft failure (73–75). However, the so-called marginal donor organs are associated with good outcome if the pancreas, on inspection, is found to be “healthy” in appearance (76,77).

Donors after cardiac death (DCD) are being used increasingly to expand the donor pool. However, there may be a higher rate of early organ dysfunction with these donors (78). A recent survey showed equivalent patient and graft survival at 1, 3, and 5 years in SPK transplant recipients from DCD compared with donors after brain death (78).

**PANCREAS PRESERVATION**

UW solution was first used for pancreas preservation in a preclinical model in 1987 (79). As with most solid organs, in vivo flush followed by simple storage in cold UW solution is the standard for pancreas preservation. In the original model, pancreases were preserved for up to 96 hours (80). In clinical transplantation, pancreas cold preservation exceeding 24 hours has been associated with increased graft dysfunction (81). Even when there is less than 24 hours, it has been shown that the longer the cold ischemia time, the greater the technical complication rate (82). Therefore, every effort should be made to minimize the cold ischemia time in order to optimize graft function and to lower complication rates. Recent data suggest a new method of preservation that may be advantageous: the two-layer method using UW solution and perfluorochemical (83). This method allows for longer preservation time while providing a mechanism for repair of ischemic damage due to cold storage (84–86). More clinical trials are needed before the two-layer method becomes routine.

Recently, histidine-tryptophan keto glutarate solution has been increasingly used in pancreas transplantation (87). Advantages include lower viscosity, less potassium, and lower cost. Early outcome studies do not show inferiority compared to the more expensive UW solution (88,89).

**HUMAN LEUKOCYTE ANTIGEN MATCHING**

The impact of human leukocyte antigen (HLA) matching on outcome varies. It is generally accepted that HLA matching has little effect on graft outcome for the SPK category (90,91), although higher rejection rates have been reported with poor matches (92–94). For solitary pancreas transplants (PAK and PTA), the data are mixed, ranging from studies showing no impact (95) to registry data showing that HLA A and B matches have a significant impact (91). At the University of Minnesota, SPKs are done regardless of HLA match; for PAKs, generally at least one antigen in the B locus matches, and for PTAs, at least one antigen in each of the A, B, and DR loci matches.
ANESTHETIC CONSIDERATIONS

A patient with brittle diabetes and secondary complications (e.g., CAD, autonomic neuropathy) can pose special problems for the anesthesiologist. Dysautonomic response to drugs or hypoxia can lead to significant morbidity and even death (96). It has also been documented that long-standing diabetes poses a challenge to the anesthesiologist during intubation (97). Awareness of these risks and employment of an experienced anesthesiology team might help decrease the risks or morbidity. A major operation such as a pancreas transplant or combined kidney–pancreas transplant is often prolonged and can be associated with significant blood loss. Prompt replacement with blood or colloid should be instituted to avoid hypoperfusion after significant blood loss. Before and after revascularization of the pancreas, careful blood glucose monitoring, along with continuous intravenous (IV) insulin therapy to maintain tight control of blood glucose levels, is essential. Perioperative β-blockade should be considered for long-standing diabetic patients with a cardiac history.

BACK-TABLE PREPARATION OF THE DONOR PANCREAS

Once the donor pancreas has been opened in the recipient operating room, some back-table work is necessary to prepare it for the transplant, including these steps (98):

1. Donor splenectomy (taking care to avoid injury to the pancreatic tail)
2. Trimming down of the donor duodenum to the shortest length without damage to the main or accessory duct (especially important with BD to minimize bicarbonate loss)
3. Oversewing or individual vessel ligation of the mesocolic and mesenteric stumps on the anterior aspect of the pancreas
4. Excision of lymphatic and ganglionic tissue in the peripancreatic area
5. Reconstruction of the splenic and superior mesenteric arteries with a Y graft of the donor iliac A bifurcation (to provide for a single arterial anastomosis in the recipient).

RECIPIENT OPERATION

Several techniques have been described for the recipient operation (32,99). The techniques vary based on whether a solitary pancreas transplant (PTA, PAK) or a combined transplant (SPK) is done.

Solitary Pancreas Transplant

Choice of Exocrine Secretion of the Pancreas—Drainage of Bowel or Bladder?

Currently, for pancreas transplants in the United States, 86% of PAK, 79% of PTA, and 87% of SPK transplants are drained enterically (5,6). ED is more physiologic and does away with the complications of BD (e.g., acidosis, pancreatitis, urinary infections, hematuria). Between 10% and 20% of BD recipients are ultimately converted to ED because of such complications once they are 6 to 12 months posttransplant and their rejection risk is lower. BD, however, allows for direct measurement of urinary amylase as a marker of exocrine function. A decrease in urine amylase is sensitive, but not very specific, for acute rejection of the pancreas (100,101). Hyperglycemia is a late event in the rejection, and a decrease in urine amylase occurs early. Thus, rejection episodes are detected early with BD, and the rejection loss rate is lower with BD than with other techniques (55). In clinical practice, the choice of exocrine drainage varies. Some groups always use ED, while some always use BD (101,102). Others base it on the individual recipient’s immunologic risk versus the risk of urologic complications (28). The surgical risks and short-term outcome with both techniques are comparable (74,103). ED is likely to predominate as the major technique in the future as immunologic strategies to eliminate rejection are developed (102).

Choice of Venous Drainage—Portal or Systemic?

Currently in the United States, of all ED transplants, 20% of SPK, 10% of PAK, and 12% of PTA cases are drained to the portal vein (5,6). Portal drainage is more physiologic than systemic drainage (104,105). Theoretically, portal drainage preserves the first-pass metabolism of insulin in the liver. Therefore, portally drained recipients will have lower systemic insulin levels (106). However, there is no evidence of any detrimental effect on lipid levels (107) or on risk of vascular disease (62) as seen in de novo hyperinsulinemia (syndrome X). Portal venous drainage is difficult to perform with exocrine BD (45). Portal drainage had gained in popularity after initial reports that rejection rates are lower in this category (103,108). It appears, however, based on registry data (5,6) that the immunologic advantage is much smaller than initially found. Recent modifications include a retroperitoneal portal-ED technique (109).

Transplantation Portion—Whole Organ or a Segment?

Almost all cadaveric pancreas transplants performed today use whole-organ grafts. Segmental grafts have little role to play in this group, except when a rare anatomic abnormality is noted such that the head of the pancreas cannot be used. A rare instance of a split cadaveric pancreas transplanted into two different recipients has been described (110). All living-donor pancreas transplants use segmental grafts (body and tail); doing so maintains normoglycemia in the recipient (12).

Simultaneous Pancreas–Kidney

SPK transplants have a lower rejection rate than do solitary pancreases. Further, rejection episodes are rarely isolated to the pancreas alone. Most pancreas rejection episodes can be indirectly detected by monitoring serum creatinine as a marker for kidney rejection. Therefore, most SPK transplants are done using ED, as advocated by the Stockholm group (111) (Fig. 73.5). With ED, the risk of acute technical complications is slightly higher, but the chronic complication rate is lower (112). Choice of venous drainage varies by center. Because ED is the choice for exocrine drainage, there is no impediment to performing portal venous drainage.
POSTOPERATIVE CARE

After an uncomplicated pancreas transplant, the recipient is transferred to the postanesthesia care unit (PACU) or the surgical intensive care unit (SICU). Centers that have a specialized monitored transplant unit (with central venous and arterial monitoring capabilities) transition the postoperative recipients through the PACU to the transplant unit. Others transfer directly to the SICU for the first 24 to 48 hours. Care during the first few hours after transplant is similar to care after any major operative procedure. Careful monitoring of vital signs, central venous pressure, oxygen saturation, and hematologic and laboratory parameters is crucial. The factors below are unique to pancreas recipients and should be attended to.

Blood Glucose Levels

Any sudden, unexplained increase in glucose levels should raise the suspicion of graft thrombosis. An immediate ultrasound examination must be done to assess blood flow to the graft. Maintenance of tight glucose control (<150 mg/dL) using an IV insulin drip is important to “rest” the pancreas in the early postoperative period.

Intravascular Volume

Because the pancreas is a “low-flow” organ, intravascular volume must be maintained to provide adequate perfusion to the graft. Central venous pressure monitoring is used to monitor intravascular volume status. In some cases, such as patients with depressed cardiac function, pulmonary artery catheter monitoring may be required during the first 24 to 48 hours. If the hypovolemia is associated with low hemoglobin levels, then washed packed red blood cell transfusions should be given. Otherwise, colloidal or crystalloid replacement can be used.

Maintenance IV Fluid Therapy

The choice of IV fluid is usually 5% dextrose in 0.45% saline solution. The use of dextrose is not contraindicated and may be of benefit, as long as IV insulin is used to maintain good blood glucose control. In SPK recipients, whose IV rate is based on urine output, dextrose should be eliminated if the urine output is high (>500 mL/hr). Maintenance solution for BD recipients should include 10 mEq of HCO₃ added to each liter to account for the excess HCO₃ loss (113,114); sodium lactate can be used as an alternative (115).

Antibiotic Therapy

Broad-spectrum antibiotic therapy (with strong gram-negative coverage) and antifungal therapy are instituted before the incision is made in the operating room, then continued for 3 (for antibiotics) and 7 days (for antifungal). At the University of Minnesota, since the introduction of this protocol, we have noted a decrease in postoperative abdominal infections (74). Cytomegalovirus (CMV) and antiviral prophylaxis are similar to that for other solid organs.

Octreotide

The use of octreotide in pancreas recipients helps reduce the incidence of technical complications (116). This benefit should be weighed against evidence from rat studies that shows decreased pancreatic islet blood flow with octreotide use (117), although clinically no detrimental effects of octreotide use have been documented. A dose of 100 to 150 μg IV or subcutaneously three times a day is administered for 5 days posttransplant. Dose adjustments may be made for nausea, which is the predominant side effect.

Anticoagulation

The use of low-dose heparin in the early postoperative period (days 0 to 5) decreases the risk of graft thrombosis (118). An intraoperative dose of 70 units/kg is given, followed by an IV infusion of 3 units/kg started at 4 hours postoperatively and gradually increased up to 7 units/kg (depending on hemodynamic stability and hemoglobin levels). Enteric-coated aspirin (80 mg) is started on day 1 and continued for 6 months. At the University of Minnesota, this protocol decreased the thrombosis rate from about 12% to 6%, but increased the relaparotomy rate due to bleeding from 4% to 6%. Segmental pancreas transplants (as in living-donor transplants) have a higher thrombosis risk and therefore therapeutic heparinization (with a target-activated partial thromboplastin time [aPTT] of 50 seconds) for 5 days and Coumadin therapy (with a target international normalized ratio [INR] of 2 to 2.5) are recommended for 6 months. The higher risk of thrombosis is due to the smaller vessels in a segmental graft (119,120).

IMMUNOSUPPRESSION

Immunosuppression is essential to thwart rejection in all allograft recipients (17). Before the advent of cyclosporine in the early 1980s (121), azathioprine and prednisone were the mainstays of immunosuppression. From the early 1980s to the mid-1990s, cyclosporine was added to the mix and resulted in significant improvement in immunologic outcomes (122). Since the mid-1990s, tacrolimus and mycophenolate mofetil have replaced cyclosporine and azathioprine as the main drugs, resulting in even better pancreas graft survival rates (122–124). In addition, steroids have been successfully withdrawn from some pancreas recipients (125) and, in some cases, avoided (126). With a recently introduced drug, rapamycin, used in combination with tacrolimus, steroids have been successfully avoided in some pancreas recipients (127,128).

Anti-T-cell therapy has always remained a part of the induction protocol for pancreas recipients. With the recent emphasis on steroid withdrawal or avoidance, anti-T-cell therapy has taken on added importance to avoid rejection. Anti-CD25 antibodies are also used frequently as induction therapy (129). Avoidance of calcineurin inhibitors has been attempted in pancreas transplantation. When combined with steroid avoidance, this required prolonged anti-T-cell therapy, which increases the risk of infection without adequately controlling rejection (130). Table 73.2 presents the immunosuppressive protocol for pancreas transplant recipients at the University of Minnesota.

For PTA recipients, whose rejection rates are the highest of all categories, pretransplant immunosuppression has decreased rejection rates and graft loss from rejection (31).
Heavy use of immunosuppression may increase the infection rate, but effective antimicrobial prophylaxis has helped ameliorate this problem (131,132).

INTRAVENTOUS IMMUNOGLOBULIN AND PLASMAPHERESIS

IV immunoglobulin has many applications in transplantation. It has been used successfully to decrease anti-HLA antibodies in transplant recipients on the waiting list and to shorten their waiting times (133,134). It can also be used to control acute humoral rejection in kidney and heart allograft recipients (135). Plasmapheresis has been used to decrease humoral antibody titers in ABO-incompatible liver and kidney recipients (136,137). It has also been used to control hyperacute and accelerated acute rejection in positive cross-match kidney recipients (138,139) and lung (140) recipients. At the University of Minnesota, for ABO-incompatible (A2 to O, B, or AB) or positive cross-match (T-cell) pancreas recipients, the treatment protocol consists of intraoperative IV immunoglobulin (0.5 mg/kg) followed by a course of 5 to 7 days in combination with daily plasmapheresis. For B-cell positive cross-match recipients, IV immunoglobulin may be used without plasmapheresis.

SURGICAL COMPLICATIONS

Bleeding

Postoperative bleeding is a frequent reason for early relaparotomy in pancreas recipients. The incidence ranges from 6% to 8% (74,141). This risk is increased by the use of anticoagulation in the immediate postoperative period. Frequent physical examinations and monitoring of hemoglobin help detect bleeding early. Heparin may be temporarily suspended to stabilize the patient. If bleeding continues, early operative intervention is indicated. If bleeding stops or slows down, heparin should be restarted at a lower rate and judiciously increased as tolerated.

Thrombosis

The incidence of thrombosis posttransplant ranges from 5% to 13% (118,141). The risk is increased after segmental pancreas transplants because of the small caliber of vessels (51). Most thromboses are due to technical reasons. A short portal vein (requiring an extension graft) or atherosclerotic arteries in the pancreas graft increases the risk for thrombosis. In the recipient, a narrow pelvic inlet with a deeply placed iliac vein, atherosclerotic disease of the iliac artery, a technically difficult vascular anastomosis, kinking of the vein by the pancreas graft, significant hematoma formation around the vascular anastomosis, and a hypercoagulable state are some of the factors that increase the risk for thrombosis. The most common form of hypercoagulable state is factor V Leiden mutation in the Western population. The incidence ranges from 2% to 5% but may be as high as 50% to 60% in patients with a history (self or family) of thrombosis (142). Other causes of hypercoagulable state include antithrombin deficiency, protein C or S deficiency, activated protein C resistance, and anticardiolipin antibodies (143).

Duodenal Leaks

The incidence of duodenal leaks ranges from 4% to 6% (74,141). A leak from the anastomosis of the duodenum to the bowel almost always leads to a relaparotomy. Gross
peritoneal contamination due to an enteric leak necessitates a graft pancreatectomy. The diagnosis is made by elevated pancreatic enzymes associated with acute abdomen. The differential diagnosis is pancreatitis, abdominal infection, or acute severe rejection. A Roux-en-Y anastomosis to the pancreaticoduodenum may be preferred if the risk of leak is thought to be increased during intraoperative inspection of the pancreas. Other novel techniques such as a venting jejunostomy (Roux-en-Y) have been used in selected recipients (144). Duodenal leaks in BD recipients are usually managed nonoperatively with prolonged catheter decompression of the urinary bladder. The diagnosis is made using plain or computed tomography (CT) cystography. The size and extent of the leak cannot always be assessed by the imaging studies. Large leaks may require operative intervention, such as a repair or enteric conversion (145).

**Major Intra-Abdominal Infections**

The incidence of intra-abdominal infections requiring reoperation ranges from 4% to 10% (74,141). Opening the duodenal segment intraoperatively, with associated contamination, predisposes to this high rate; fungal and gram-negative infections predominate. With the advent of advanced intervenational radiologic procedures to drain intra-abdominal abscesses, the incidence of reoperations is fast decreasing. If the infection is uncontrolled or widespread, then graft pancreatectomy followed by frequent washouts may be necessary.

**Renal Pedicle Torsion**

Torsion of the kidney has been reported after the SPK transplants (146,147). The intraperitoneal location of the kidney (allowing for more mobility) predisposes to this complication. Additional risk factors are a long renal pedicle (>5 cm) and a marked discrepancy between the length of artery and vein. Prophylactic nephropexy to the anterior or lateral abdominal wall is recommended in intraperitoneal transplants to avoid this problem.

**Others**

Other surgical complications that may require laparotomy also decreased from 9% to 1%. Improved anti-infective prophylaxis, surgical techniques, immunosuppression, and advances in interventional radiology have all contributed to this disease (74).

**NONSURGICAL COMPLICATIONS**

**Pancreatitis**

The incidence of posttransplant pancreatitis varies based on the type of exocrine drainage. BD recipients with abnormal bladder function are at increased risk secondary to incomplete bladder emptying or urine retention causing resistance to the flow of pancreatic exocrine secretions. Other causes of pancreatitis include drugs (corticosteroids, azathioprine, cyclosporine), hypercalcemia, viral infections (CMV or hepatitis C), and reperfusion injury after prolonged ischemia. Pancreatitis is usually manifested by an increase in serum amylase and lipase with or without local signs of inflammation. The treatment usually consists of catheter decompression of the bladder for a period of 2 to 6 weeks, depending on the severity. In addition, octreotide therapy may be used to decrease pancreatic secretions. The underlying urologic problem, if any, should be treated. If repeated episodes of pancreatitis occur, an enteric conversion of exocrine drainage may be indicated (148–150).

**Rejection**

The incidence of rejection is discussed in the Results section earlier in this chapter. The diagnosis is usually based on an increase in serum amylase and lipase and a decrease in urine amylase in BD recipients. A sustained significant drop in urinary amylase from baseline should prompt a pancreas biopsy to rule out rejection (151). In ED recipients, one has to rely on serum amylase and lipase only. A rise in serum lipase has recently shown to correlate well with acute pancreas rejection (149). Other signs and symptoms include tenderness over the graft, unexplained fever, and hyperglycemia (usually a late finding). Diagnosis can be confirmed by a percutaneous pancreas biopsy (152–154). In cases in which percutaneous biopsy is not possible due to technical reasons, empiric therapy may be started. Rarely, open biopsy is indicated. Transcystoscopic biopsy, which was used in the past, has been largely abandoned.

**Others**

Other findings include infectious complications such as CMV, hepatitis C, extra-abdominal bacterial or fungal infections, posttransplant malignancy such as posttransplant lymphoproliferative disorder, and other rare complications such as graft-versus-host disease that occur in pancreas transplantation. The diagnosis and management of these complications are similar to those of other solid-organ transplants.

**FUTURE DIRECTIONS**

In diabetic patients with kidney dysfunction, SPK or PAK transplant is the standard of care. A PTA, however, is less common because the long-term risks of diabetes are pitted against the long-term risks of immunosuppression. A successful transplant can improve existing neuropathy (62) in diabetic recipients, and the survival after a solitary pancreas transplant is better than remaining on the waiting list (65). As the risks of immunosuppression decrease with novel methods of tolerance and immunomodulation (102), the balance will tilt in favor of an early transplant. The limiting factor will then be the organ shortage, which could be alleviated if xenotransplantation is able to overcome its current barrier of hyperacute rejection (155).

The application of islet transplants is rapidly growing. Recent successes (7,8) suggest that islet transplants can provide all the benefits of pancreas transplants without the risks of major surgery. Xenotransplantation of islets may be more readily achievable using encapsulation (156) than with other organs. Prolonged diabetes reversal after intraportal xenotransplant in primates has been documented (157) and may pave the way for human xenotransplant trials. Also, stem cells that are manipulated to differentiate into islets may provide a rich supply for transplantation (158). Islet transplants can be combined
with immunomodulation and tolerogenic strategies to minimize or avoid immunosuppression (159). This combination would provide for minimally invasive cellular (islet) transplants for all type 1 diabetic patients without the need for long-term immunosuppression. But unless the results of clinical islet transplantation continue to substantially improve, pancreas transplantation remains the best treatment option long-term for (labile) type 1 diabetic patients with or without uremia.

Key Points

1. Pancreas transplantation remains the most reliable treatment option for insulin-dependent patients with diabetes that offers freedom from insulin administration long-term and achieves normoglycemia.
2. Pancreas transplantation can hold or even reverse some of the secondary complications of diabetes mellitus.
3. Pancreas transplants can be performed in (a) nonuremic, brittle diabetic patients, (b) uremic diabetic patients, and (c) posturemic diabetic patients who underwent a previous kidney transplant.
4. One-year patient survival rates after pancreas transplantation are over 95%, graft survival rates are above 80%.
5. Quality of life is markedly improved in previously diabetic patients after successful pancreas transplantation.
6. Graft loss from technical or immunologic complications is less than 5% each at 1 year.

References

2. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. JAMA. 1997;277:372.


