9

Postoperative Management

9.1

Uncomplicated Course

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A complication-free outcome after a pancreas transplant depends on detailed knowledge of both the recipient and donor. To minimize morbidity, postoperative care actually begins pre- and intraoperatively (see chapters 7 and 8). Transplant surgeons and physicians must anticipate the expected graft function and patient response to the operative procedure. Failure to do so will prolong the hospital stay and possibly compromise graft and patient survival. For example, if delayed kidney graft function is expected after a simultaneous pancreas and kidney (SPK) transplant pre- and intraoperative decisions can be made regarding fluid restriction, the need for early dialysis, and the choice of immunosuppressive agents. This chapter provides insight into the key elements necessary for the early management of pancreas transplants postoperatively, with emphasis on avoiding preventable complications.

Preoperative Care

As with any surgical procedure, detailed knowledge of the patient is essential. A meticulous preoperative evaluation, including a complete history and physical examination, is crucial to ensure optimal patient and graft outcomes. Preoperative evaluation also allows for assessment of acute medical issues (e.g., infectious diseases) that would contraindicate surgery. In pancreas transplant recipients, significant emphasis must be placed on three areas: (1) cardiovascular status, (2) kidney function, and (3) glucose control.

Immediate preoperative cardiac evaluation is pivotal because most pancreas transplant recipients have had insulin-dependent diabetes for 20 years or more. Underlying cardiac disease should be presumed, even if recent cardiac testing (stress tests or catheterization) indicates otherwise. One would assume that patients with relatively negative cardiac testing should fare better than those with significant disease. However, it is our opinion that *all* patients undergoing pancreas transplantation are at risk for a cardiac event; thus, all should be managed to maintain optimal cardiac status (i.e., balanc-

ing cardiac output and perfusion pressure while minimizing cardiac oxygen demand).

Previous hospital records pertaining to cardiac evaluations and procedures (e.g., angioplasty, bypass) should be reviewed as early as possible. Commonly, a significant amount of time (months to years) may have passed since a potential candidate's initial evaluation. For this reason, patients should undergo appropriate cardiovascular evaluation every 6 months to 1 year while on the waiting list.

If, on preoperative admission, significant progression of cardiac disease is diagnosed (based on recent medical history, physical examination, or electrocardiogram [EKG]), it may be necessary to proceed with additional noninvasive stress testing or directly with coronary arteriography. If revascularization (i.e., coronary artery bypass) is indicated, the pancreas transplant should be deferred.

Because diabetic micro- and macroangiopathy is in a relative state of progression (the degree of which varies from patient to patient), attention must also be given to peripheral vascular disease. Details must be obtained during the admission history and physical examination regarding vasculopathy, especially with respect to aortoiliac atherosclerosis. Preoperative, detailed knowledge of vascular lesion(s) is imperative so that proper dissection can be performed for the arterial anastomotic sites.

For those patients who have had a significant change in their peripheral vascular examination, immediate duplex ultrasonography, magnetic resonance angiogram (MRA), or arteriography should be considered. If, on preoperative admission, significant, unexpected disease is identified at the level of the iliac arteries, the patient may require repair (bypass, angioplasty) during the transplant procedure or the transplant should be deferred until all lesions have been corrected. In general, if the immediate preoperative evaluation demonstrates new and significant progression of cardiovascular disease it is usually wiser to choose another recipient rather than take the risk of trying to "finesse" a possibly doomed transplant.

As with arterial evaluation, a complete history of venous catheterizations and anomalies should also be obtained to avoid undue delays intraoperatively with central venous catheter placement.

In uremic candidates, the need for hemodialysis must be determined prior to transplantation. In this context, knowledge of dialysis status and preoperative fluid management (including electrolyte, acid base, and volume status) is vital to the proper choice of a uremic recipient for organs from a particular donor. Special attention should be given to recipient potassium; if levels are high, a rapid decision must be made to treat medically or with dialysis. Patients who are fluid overloaded, have high potassium levels, and/or are inadequately managed by peritoneal dialysis (i.e., imbalance of metabolic profile and/or chronic state of fluid overload) may require a course of hemodialysis immediately prior to surgery. Adequate pretransplant hemodialysis not only simplifies perioperative management but also reduces the risk of hyperkalemia during surgery. Although pretransplant hemodialysis prolongs ischemic time, those patients then will not require immediate posttransplant dialysis, which carries with it the risks of bleeding (due to heparinization), hypotension, and acute tubular necrosis (ATN) if the kidney graft fails to function immediately. Thus, adequate time should be allowed to optimize the recipient's fluid and electrolyte status via hemodialysis if necessary. The duration of pretransplant hemodialysis should be discussed by the transplant surgeon and nephrologist to minimize the surgical risk as well as minimize graft cold ischemic time so as to not compromise graft function.¹

If the transplant candidate is on peritoneal dialysis, peritonitis should be ruled out by gram stain examination. Typically, definitive culture results are pending before the transplant procedure is started.

Another important area of evaluation is glucose control. Because potential recipients are nothing per os (NPO) prior to surgery, close monitoring of blood sugar is mandatory. Many patients will have administered their long-acting insulin prior to notification of the possible transplant. They are usually kept NPO prior to hospital arrival and thus require a finger-stick glucometer reading upon admission. A laboratory blood glucose level is also obtained to confirm glucose status. To properly manage blood sugars, a peripheral intravenous (IV) line should be placed immediately. Although variations exist from center to center on how to best manage blood sugar (either sliding scale or insulin drip), the underlying theme of all protocols is to pay close attention (usually hourly). Surgeons and anesthesiologists must adequately communicate so that optimal glucose control is maintained throughout surgery. In the event that a patient has not administered their regularly scheduled insulin dose at the time of transplant notification, one third to one half the usual dose is recommended while the patient is NPO.

In the hours following hospital admission, the house staff must optimize this period for the final preoperative evaluation and preparation of the patient (Table 9.1.1). In general, and specifically for SPK and pancreas after kidney (PAK) re-

TABLE 9.1.1. Immediate preoperative evaluation of pancreas recipients.

1. Review of transplant work-up results
Cardiovascular testing
• Electrocardiogram
• Stress echocardiogram (mandatory for >20 y of IDDM)
• Cardiac catheterization (if done)
• Peripheral vascular noninvasive studies (if done)
• Aortogram with peripheral runoff (if done)
• Previous venous catheters, fistulas, grafts, and complications
Noncardiac testing
• Mode and adequacy of dialysis
• Abdominal ultrasound
• Chest x-ray
• Pulmonary function tests (if done)
• Sigmoidoscopy or colonoscopy (mandatory for age >50 y)
• Cystourethrogram (if history of infection, congenital abnormality, reflux, or neurogenic bladder)
• Dental exam
• Ophthalmology exam
• Females: Last pelvic exam with Pap smear and mammogram (if needed)
Psychosocial evaluation
2. History and physical
With emphasis on changes in cardiovascular disease, infectious history (including viral), dialysis access and needs, previous surgery
3. Admission testing
Chest x-ray
Electrocardiogram
Laboratory tests
ABO type and antibody screen
Type and screen for blood transfusion
Histocompatibility: Crossmatch and panel-reactive antibody assessment
Complete blood count
Complete metabolic panel
Coagulation factors
Hepatitis panel (A, B, C)
HIV
Viral panel (EBV, CMV, HSV, VZV)
RPR
PSA (for males age 55 and older)
Serum pregnancy (for females <55)
Urine analysis

IDDM, insulin-dependent diabetes mellitus; HIV, human immunodeficiency virus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; VZV, varicella-zoster virus; RPR, rapid plasma reagin; PSA, prostate-specific antigen.

cipients, the preparation phase is similar to that of kidney transplant alone (KTA) recipients. This period usually ranges from a minimum of 3 to 5 hours due to the time required by the histocompatibility laboratory to complete the crossmatch. The preoperative orders (Table 9.1.2) should be complete and the results of all admission tests reviewed. Ample time is available for a preoperative shower with hibiclens or betadine. A rectal enema should be given early to ensure evacuation of fecal content. Dialogue with the patient regarding the expected risks and benefits of the surgical procedure must take place and conclude with the signing of consent. This time also allows the patient to be reintroduced to any clinical studies for which they are eligible. To maximize communication

TABLE 9.1.2. Template for routine admission orders.

1. Admit to transplant unit
2. Notify transplant housestaff on-call of patient arrival
3. Notify staff nephrologist on-call for dialysis orders (if necessary)
4. Send transplant evaluation chart to floor
5. Sign preoperative consent
6. Notify study coordinator of patient arrival
7. If patient on peritoneal dialysis, drain dialysate from abdomen prior to OR
8. Assess vital signs Q 4 h
9. Record weight and height
10. Strict monitoring of intake and output
11. Shower patient with hibiclens or betadine
12. Administer warm tap water enema per rectum $\times$ 2; notify MD if no results
13. Keep NPO except medications with sips of water
14. Apply heel protectors prior to transfer to OR; pneumomatic compression garment to OR
15. Obtain finger-stick blood sugars Q 1 h times 2, then Q 2 h when stable
16. Begin immunosuppression (per protocol)
17. Send antibiotics to be given in OR (per protocol)
18. Admission testing (as detailed in Table 9.1.1)

OR, operating room.

in this regard, patients should become aware of the possibility of study entry at the time of listing. To maximize information transfer and patient accrual, personnel most familiar with a particular experimental protocol should conduct the discussion and consent process.

Intraoperative Care

Successful intraoperative management depends on cooperation and team work between the surgeons, anesthesiologists, and nursing staff involved. A brief description appears here while a more detailed discussion is provided in chapter 8.2.1. A nasogastric tube and bladder catheter should be placed immediately following the onset of anesthesia and intubation. Most centers prefer placement of a central venous line (preferably internal jugular) for volume status monitoring (central venous pressure [CVP]) while others are most comfortable with pulmonary artery catheters (Swan-Ganz). Similarly, institutional preferences vary with respect to the need for an arterial line compared to arm cuff for monitoring blood pressure. Pulmonary artery catheters and arterial lines are most commonly used in recipients with compromised cardiovascular status.

Prior to the incision, appropriate antibiotics and immunosuppressants are administered per protocol; intraoperatively, antibiotics may need to be redosed. Fluids (electrolyte solutions and colloids) are administered to maintain a CVP in the 12- to 15-mm Hg range. Most centers prefer colloid to minimize the amount of total fluids given which possibly aids in reducing postoperative fluid overload. Blood glucose is monitored hourly and usually controlled with an insulin drip; blood glucose levels should be maintained at 110 to 150 mg/dL.

At the time of organ reperfusion, bleeding from the allograft(s) may be problematic, especially from the pancreas.

Adequate volume status is imperative at this time point. Aggressive use of blood products may be required, so adequate communication and preparation by the anesthesiology and nursing staffs must ensure that immediate infusion can begin if necessary. In nonuremic, PAK or pancreas transplant alone (PTA) recipients, 30 U/kg of IV heparin is recommended by some centers to prevent pancreatic vascular thrombosis and is given just prior to reperfusion of the pancreas.^{2,3} Simultaneous pancreas and kidney recipients are rarely heparinized at the time of revascularization (unless the recipient has a previous history of deep venous thrombosis or pulmonary embolism). Before revascularization, diuretics are frequently given to promote early kidney graft function in SPK recipients (using furosemide) and reduce pancreas graft swelling (using mannitol up to 1 g/kg). Some centers also recommend the use of somatostatin analogs.

Upon completion of the procedure, the abdomen is copiously irrigated with antimicrobial solutions (e.g., containing bacitracin and amphotericin). Closed-suction drains are rarely placed and are usually reserved for situations where allograft trauma is suspected that may result in bleeding or pancreatic leak. A suction and drainage system (chapter 8.2.2) may be placed in case of severe pancreatitis after revascularization. The abdomen and skin are then closed and the patient prepared for transfer from the operating room.

Immediate Postoperative Care

Immediately following the transplant, recipients are brought to the postanesthesia care unit or intensive care unit (ICU). As with any surgical procedure, hemodynamic and ventilatory assessment is paramount during recovery. In most instances, the endotracheal tube can be removed in the operating room. However, one should not fret about leaving the patient intubated while awaiting further evaluation in the recovery unit. A blood gas demonstrating adequate gas exchange, a stable blood pressure and pulse rate, good urine output, adequate pain control, and a satisfactory chest x-ray are all indicators that a patient can be successfully extubated, recovered, and sent to the desired ward (either ICU or monitored step-down unit). However, if liberal use of IV fluids occurred during the operative procedure facial and laryngeal edema as well as pulmonary fluid overload may be a concern and preclude early extubation. A complete blood count, complete chemistry and coagulation profiles, chest radiograph, and EKG are routinely obtained. Vital signs and oxygen saturation are monitored frequently.

Early Graft Function: Days 1 and 2

The first 24 to 48 hours posttransplant are the most crucial. It is during this period that recipients are most vulnerable and at highest risk for a catastrophic error in postoperative care.

TABLE 9.1.3. Template for routine postoperative orders.

1. Admit to ICU (or step-down unit)
2. Condition: Critical
3. Allergies:
4. Vitals signs per intensive care protocol: Notify MD for SBP > 160 or <120, DBP > 100, HR > 120 or <60, temperature > 101.5°F, RR > 25 or <10
5. Activity: Bedrest × 24 h, then OOB to chair QID
6. Nursing specials
 - Cardiac monitor
 - CVP or Swan-Ganz catheter to monitor; notify MD for CVP > 15 or <8 mm Hg
 - BP cuff Q 5 min or arterial line to monitor
 - Continuous-pulse oximetry; titrate O₂ to keeps saturation above 93%
 - NGT to low intermittent suction
 - Foley catheter to gravity. Irrigate Foley w/30 cc NS prn for clot removal. Notify MD if CBI possibly required.
 - Strict input & output Q 1 h
 - Drains to bulb suction (if present). Measure output Q 4 h & prn
 - Elevate head to 30°
 - Incentive spirometry Q 1 h
 - Pneumatic compression garments to legs bilaterally
 - Abdominal binder when patient upright
 - Q 1 h accuchecks while patient on insulin drip. Titrate to keep BGs between 100–150.
7. Diet: NPO
8. IV fluid
 - Replacement fluid 1/2 NS with 10 meq HCO₃⁻ at cc/cc output (h)
 - If urine output > 1000 cc/h, then replace 1/2 cc/cc
 - If urine output < 100 cc/h, call MD
 - Maintenance of D5 1/2 NS at 50 cc/h (optional, must subtract from replacement)
9. Medications*
 - Pain medication: Patient-controlled pump (morphine, dilaudid)
 - Antibiotics
 - Immunosuppression
 - Gastric antisecretory agent
 - Nystatin swish & swallow
 - CMV prophylaxis (gancyclovir or valacyclovir; adjust dose for renal function)
 - Beta blocker PRN
 - Dopamine (if needed)
 - Sulfamethoxazole/trimethoprim
 - Octreotide (optional)
 - Rectal laxative (begin POD 2)
 - Stool softener when taking PO
 - Females: Antifungal vaginal suppository
 - Other medications based on patient's preoperative history
10. Labs
 - In PACU: Complete blood count, basic metabolic panel, calcium, magnesium, amylase, lipase, coagulation factors
 - First 24 h: CBC, BMP, Ca⁺⁺, Mg⁺⁺ Q 6 h × 3
 - Daily labs: CBC, BMP, serum amylase & lipase, FK or CSA level; urinary amylase (bladder drained only)
11. CXR in recovery room
12. Begin self-medication teaching on POD 1 or as soon as able

DBP, diastolic blood pressure; HR, heart rate; RR, respiration rate; OOB, out of bed; QID, once daily; BP, blood pressure; NGT, nasogastric tube; NS prn, normal saline as needed; CBI, continous bladder irrigation; BG, blood gases; POD, postoperative day; PO, per os (orally); PACU, postoperative after-care unit; CBC, complete blood count; BMP, basic metabolic panel; FK, tacrolimus; CSA, cyclosporine; CXR, chest x-ray.

*See discussion in text for medication recommendations.

In short, the goal is to support the patient's body systems in maintaining a steady state during a period when fluid shifts and medical management are most difficult. In this phase of recovery, three major processes are evolving: (1) The recipient is undergoing the physiological response to surgical trauma, (2) the transplanted organs are in a varying degree of reperfusion injury/recovery (including reperfusion pancreatitis), and (3) the recipient is now immunosuppressed. As one can expect, the combination of these three processes, especially in a diabetic patient with significant secondary complications of their disease, presents a formidable challenge to the transplant team.

In the following sections of this chapter, detailed information is provided on the specifics of posttransplant care of pancreas transplant recipients. Emphasis is placed on the complexity of the posttransplant process in diabetic recipients and on strategies to avoid the consequences of suboptimal management that lead to early graft loss and increased patient morbidity. A template for routine postoperative orders is provided in Table 9.1.3.

IV Volume Monitoring and Fluid Management

Due to the long history of diabetes in pancreas transplant recipients, one can presume that coronary and peripheral vascular compliance is compromised. Therefore, individual recipients may have a narrower "window" of optimal volume status compared to nondiabetic, nonrenal failure patients. Most centers rely on CVP monitoring as a means of assessing volume status postoperatively. In most cases, a CVP between 8 to 14 mm Hg is adequate. However, emphasis must be placed on treating the patient and not the "numbers." For instance, a hemodynamically stable patient with a CVP of 5 mm Hg and good urine output may not necessarily require additional fluid. In cases where uncertainty remains regarding volume status with CVP monitoring, pulmonary artery pressure (PAP) monitoring may be warranted.

The maintenance solution commonly used following pancreas transplantation is 1/2 NS with 10 meq/HCO₃⁻. By tradition, bicarbonate replacement has been especially important for recipients with bladder drainage of pancreatic exocrine secretions.⁴⁻⁶ However, in our experience, even enteric-drained SPK recipients have an acidosis that requires bicarbonate replacement in the immediate postoperative period. Bladder-drained recipients usually require long-term, oral bicarbonate supplementation. However, the base deficit arising in enteric-drained recipients is usually self-limited due to physiological absorption of bicarbonate, and thus does not require replacement beyond the perioperative period. Maintenance fluids are usually infused at an In = Out rate once hemodynamic stability is obtained. I=O infusion is usually maintained for the first 24 hours, incorporating the above guidelines with CVP monitoring. Because of this approach, dextrose (D5) is not added to the maintenance or replacement fluids (unless the blood glucose level drops below 100 mg/dL). For recipients

of a combined kidney and pancreas where the creatinine plateaus early or in situations of a concerning cardiac history, replacement is adjusted to $1/2$ cc/cc output. After the first 24 hours, most patients are converted to a straight rate of IV fluid ranging from 75 to 150 cc/h depending on the recipient's size and volume status. Pancreas after kidney and PTA recipients usually do not have large fluid requirements and in general are more stable with respect to volume status in the uncomplicated postoperative course.

Some centers maintain a continuous rate of a D5 solution (30 to 50 cc/h) to supply a low dose of carbohydrate. We prefer to avoid dextrose in the immediate postoperative period. Dextrose may confound the understanding of pancreatic endocrine function in the early hours following the transplant. An insulin drip started intraoperatively can usually be weaned within the first 6 to 12 hours when a continuous infusion of dextrose is not administered. A dextrose infusion may unnecessarily prolong the use of an insulin drip. When in use, an insulin drip should be infused at a rate to keep the blood sugar less than 150 mg/dL.⁷ Aggressive use of insulin (blood sugars <100 mg/dL) early on in the postoperative period is not recommended due to the risk of over-administration. Inadvertent hypoglycemia can be catastrophic to the allograft(s) and patient should an insulin reaction (and the associated sequelae) occur during this period.

Electrolyte Management

Salt and mineral balance is not usually difficult postoperatively, especially with early graft function. However, when delayed graft function occurs following SPK transplantation potassium, calcium, and phosphorus balance may become problematic. Early dialysis may be necessary for hyperkalemia.⁸ Great care must be taken to properly dialyze potassium without removing too much fluid as to render the patient hypotensive (which might increase the risk of early arterial thrombosis). For patients who are hypokalemic, potassium is administered on a supplemental basis. With I=O infusion of fluids, inadvertent hyperkalemia could develop if potassium is added to the maintenance or replacement fluid (especially for recipients with urine output >1 L/h). Sodium and chloride are usually stable in this patient population and rarely is intervention required to maintain a steady state.

The role of bicarbonate replacement was previously discussed. However, additional supplementation beyond the maintenance fluid may be required for previously dialysis-dependent patients who are chronically acidotic. Ionized calcium levels should be followed to maintain an appropriate calcium state. Further, magnesium levels should be maintained above 2 mg/dL according to current cardiac recommendations.⁹ Early stabilization of potassium, calcium, and magnesium will minimize cardiac irritability and help reduce risks for a cardiac event. Although many SPK recipients may have had problems with *hyperphosphatemia* while on dialysis, *hypophosphatemia* usually ensues with good renal graft

function. Abnormal phosphorus levels are usually self-limited and correct spontaneously once the recipient begins an oral diet. However, the need for a phosphate binder or phosphate supplementation may be necessary for extreme abnormalities, delayed graft function, or high-output ATN. Aggressive management of phosphorus is usually not required because adverse consequences of abnormal phosphorus levels are extremely rare.

Blood Products and Anticoagulation

Judicious use of blood products is a necessary component to the postoperative management of the pancreas transplant recipient and must be considered to avoid or correct hypotension and tachycardia. Given the cardiac fragility of this patient population, oxygen-carrying capacity must be maximized. Most pancreas recipients are anemic prior to surgery, thus every effort should be made to maintain an adequate hemoglobin (Hgb)/hematocrit. Our preference is to maintain a Hgb >10 mg/dL. Because postoperative hemorrhage is a known complication of pancreas transplantation (see chapter 9.2.2), adequate red blood cell (RBC) volume is imperative should such an event occur and the patient require re-exploration.¹⁰

Controversy remains regarding the necessity for early postoperative anticoagulation, in particular in uremic SPK recipients.^{2,3,10} Most centers advocate low-dose IV (partial thromboplastin time [PTT] no greater than $1.5\times$ normal) or subcutaneous (SQ) heparin for nonuremic PTA and PAK recipients. Low-dose aspirin is then overlapped for 2 days prior to cessation of heparin and continued long-term upon hospital discharge. If an IV heparin drip is used postoperatively, a delay of approximately 4 hours after surgery may be necessary to determine hemodynamic stability. Frequent monitoring of coagulation parameters (PTT, international normalized ratio [INR], prothrombin time [PT], and Hgb) is required to avoid overanticoagulation. Such an error will most likely result in hemorrhage and the need for re-exploration. Postoperative hemorrhage can usually be controlled with infusion of blood products; however, one may have to accept re-exploration as a probability. The converse is avoidance of anticoagulation leading to early graft thrombosis, which usually results in graft pancreatectomy. Thus, it is better to re-explore the recipient for bleeding (which has little impact on graft function) than for thrombosis (which causes graft loss). Early use of low-molecular-weight heparin is not recommended given the unpredictable nature of this agent in the postoperative period.

After segmental pancreas transplantation, from either a living-related or cadaveric donor, initial systemic heparinization followed by coumadin therapy (for up to 6 months) is recommended. This approach is mandated by the narrower caliber of the vascular anastomoses and the associated higher risk of thrombosis.^{11,12}

For pancreas recipients with an underlying coagulopathy or liver dysfunction, fresh frozen plasma may be needed.

Rarely, desmopressin acetate (DDAVP) is required to correct platelet dysfunction resulting from uremia. However, for patients with delayed renal function in which rejection is questioned SQ administration of DDAVP may be necessary to correct prolonged bleeding time prior to obtaining a biopsy. In extreme cases, cryoprecipitate may be needed for consumptive coagulopathies resulting from hemorrhage or disseminated intravascular coagulation (secondary to massive cytokine release after revascularization). Hemorrhage secondary to severe graft pancreatitis occurs in less than 3% of all pancreas recipients.^{3,10}

Blood Pressure Monitoring

Obviously, blood pressure control is closely related to fluid and electrolyte management. Both hypo- and hypertension must be avoided. Hypotension (systolic blood pressure [SPB] < 100 mm Hg) increases the risk of arterial graft thrombosis, especially in the immediate postoperative period.¹⁰ Following surgery, graft vessels may be in spasm as a result of manipulation or reperfusion injury. Thus, hypotension in this state may result in arterial (or, less frequently, in venous) thrombosis, especially because the pancreas naturally maintains a relatively low flow state compared to other organs. Further, a low-flow state may enhance thrombus formation (either arterial or venous) at the site of a fresh anastomosis and thus increase the risk of graft loss. Severe hypotension may also compromise cardiac perfusion and result in a cerebral or cardiac event.

Prolonged hypertension, if severe enough, can also induce a cerebral vascular event or increase cardiac demand, resulting in ischemia/infarction. In addition, severe hypertension may dislodge an unstable thrombus within the operative field, resulting in intra-abdominal hemorrhage. Maintaining a systolic pressure between 120 and 160 mm Hg for the first 24 hours safely maintains graft perfusion while minimizing the risk of a serious adverse event. The use of renal-dose dopamine remains controversial.¹³ Decisive data regarding dopamine receptor agonists is still unavailable. However, if SBP remains low despite adequate fluid resuscitation, dopamine at 3 to 5 mcg/kg/min is recommended as a first-choice agent.

Prior to the transplant, most candidates are on a plethora of antihypertensive agents, usually including a calcium channel blocker, an angiotensin-converting enzyme (ACE)-inhibitor, and a beta blocker. For those whose blood pressure is extremely difficult to control, an α -1-antagonist may also be part of the regimen. Early initiation of beta blockers and α -1-antagonists may be necessary to avoid rebound hypertension and/or tachycardia. If necessary, IV labetalol or metoprolol on scheduled dosing is safe until oral beta blockers are tolerated. Similarly, sublingual or transcutaneous clonidine can be used to avoid α -1-antagonist withdrawal. In extreme cases, IV nitroglycerin or nitroprusside may be necessary for refractory hypertension. However, such measures are rarely

required in pancreas recipients with good renal function. Calcium channel blockers can also be started early.¹⁴⁻¹⁶ However, the choice of agent and dose must be carefully selected and monitored due to potential side effects. For example, verapamil interacts with calcineurin inhibitors and may increase serum levels, while amlodipine may increase fluid retention and result in edema. Angiotensin-converting enzyme inhibitors are usually withheld in the early postoperative period due to their actions on renal arteriolar vessels and the subsequent elevation of creatinine levels. However, ACE inhibitors may have a role in blood pressure management once stable graft function is obtained.¹⁷ In general, all the above agents are usually tolerated well. Before aggressive initiation of antihypertensives, orthostasis due to fluid volume shifts and/or autonomic neuropathy should be excluded. Commonly, pancreas recipients with secondary complications of insulin-dependent diabetes mellitus have pronounced autonomic neuropathy, which can produce labile blood pressures especially upon standing. Orthostatic blood pressure may indicate dehydration in bladder-drained pancreas recipients. However, if volume status is adequate and orthostatic hypotension remains problematic fludrocortisone or mineral corticoids may be warranted. Again, we cannot emphasize enough the diligence that is required for blood pressure monitoring to avoid the consequences of extreme high and low states. Constant communication is mandated between the nursing staff and various services involved with respect to this aspect of the patient's care.

Early Immunosuppression

The most critical period to obtain adequate immunosuppressive levels occurs within the first 24 to 48 hours. Immunosuppressive protocols are covered in more detail in chapter 10, so only a brief overview is presented here. Most centers give the first doses of immunosuppression within the few hours just prior to the transplant, and then continue intraoperatively. Quadruple immunosuppression is typically utilized for induction therapy, consisting of an anti-T-cell agent (first administered intraoperatively), a calcineurin inhibitor, an antimetabolite, and steroids. Tacrolimus has become the calcineurin inhibitor of choice. Mycophenolate mofetil (MMF) has virtually replaced azathioprine as the antimetabolite agent of choice. Controversy arises in the choice of antibody preparation.¹⁸⁻²³ While most centers use antilymphocyte preparations (antithymocyte globulin [ATG], OKT3, or thymoglobulin), others have adopted the use of synthetically structured, chimeric-antibody preparations designed to block interleukin-2 (IL-2) receptors (daclizumab, basiliximab); still others use a combination of antilymphocyte therapy and IL-2R blockers. The argument supporting the use of the newer synthetic agents is that they contain human Fc fragments that do not elicit the nonspecific cytokine release seen with the mono- and polyclonal preparations derived from nonhuman species. In addition, leukopenia and thrombocytopenia are common side effects of the polyclonal preparations (ATG and thy-

moglobulin). The main argument supporting antilymphocyte preparations is that lower rejection rates have been established with their use. To date, adequate experience in pancreas transplantation with anti-IL-2R has not been obtained.

Most centers agree that early levels of tacrolimus should be between 10 and 15 ng/mL with antibody induction therapy is given and above 15 ng/mL without accomplished by either IV or sublingual administration. Mycophenolate mofetil can be administered either IV or orally and titrated to 1.5 to 3 g/d (in two divided doses) depending on gastrointestinal tolerance. However, MMF should be used cautiously if induction with antilymphocyte antibody is concomitantly used secondary to the risks of profound leukopenia. Calcineurin inhibitors should be reduced dramatically or held when ATN or delayed graft function (DGF) have occurred. These agents can be resumed at full dose when adequate renal function is established (usually by a daily 20% drop in serum creatinine levels from baseline or when the creatinine drops to less than 3.0 mg/dL). High doses of steroids are administered intravenously during the first few days perioperatively and are usually tapered to 20 to 30 mg/d by the end of the first 7 to 10 days. By 6 months, most recipients should have their prednisone tapered to 5 mg or less.

Evaluation of Graft Function

Early graft function (pancreas or kidney) can be monitored by various means. Most centers adopt a protocol that combines laboratory as well as imaging studies to obtain a level of certainty with regard to adequate organ function. For some centers, declines in serum blood urea nitrogen, creatinine, amylase, and lipase levels along with normal blood sugar levels are all that is required to assess good graft function in SPK recipients.^{24–28} Some centers routinely obtain sonograms or nuclear scintigraphy on all recipients, while others may use these modalities selectively.^{29–34} Whenever graft function is uncertain, thorough examination is warranted. Ultrasonography is usually the first mode of imaging utilized to evaluate organ dysfunction, as indicated by an unexpected laboratory value or physical finding. A wealth of information can be obtained from such a cost-effective study. Ultrasonography can determine vascular abnormalities, ductal or ureteral obstruction, and the presence of periorgan fluid collections (either lymph or hematoma). The addition of a renal nuclear study complements the findings of ultrasonography by further delineating renal perfusion and clearance and determining a urinary leak. However, nuclear scintigraphy is not as useful for evaluation of the pancreas.

As portal-enteric drainage of the pancreas becomes more popular, imaging of the pancreas likewise has become more difficult, given the medial and deep position of the allograft. Unfortunately, bowel gas within loops of the small intestine and transverse colon obscure an adequate view by ultrasound (US) of the majority of the gland. In cases where the pancreatic tail is affixed to the abdominal wall, US imaging of the distal pancreatic segment may be enhanced. However, the

ability to locate the tail is limited by the experience of the technician and radiologist performing the study. Computerized axial tomography scan imaging of a portally drained pancreas can be helpful in determining peripancreatic fluid collections, pancreatic necrosis, and possibly duodenal obstruction or leak.^{30,31,33,34} The role of magnetic resonance imaging/angiography as well as positron emission tomography scanning remains to be determined.^{31,34–37}

Long-term functional monitoring begins during the recipient's initial hospitalization. As organ function steadily improves, the need for daily blood laboratory monitoring diminishes. Laboratory tests are subsequently reduced to three times per week, then two, then one, depending on individual needs. In uncomplicated, stable recipients, this process is usually an uneventful transition. Creatinine clearance and urine protein, C-peptide levels, and HbA1c can be periodically obtained to assess long-term graft function. For some pancreas transplant recipients, blood sugar levels never fully normalize despite what are believed to be adequate insulin and C-peptide levels. In such cases, glucose stimulatory tests (IV glucose tolerance test [GTT] and/or oral tolerance tests) are useful to help delineate pancreatic endocrine function. A few hypotheses attempt to explain the cause of persistent hyperglycemia or glucose intolerance following pancreas transplantation. First, the diabetogenic effects of steroids and calcineurin inhibitors (especially tacrolimus) are thought to play a significant role.³⁸ In many cases, blood sugar levels normalize as doses of these agents are reduced over time. Second, some recipients have developed an insulin resistance and are confronted with a situation no different from type 2 (adult-onset) diabetes mellitus. Third, for portal-enteric drained pancreas recipients the hepatic "first pass" of insulin may offset the hyperinsulinemic effects of systemically venous-drained pancreases. In other words, systemic venous drainage possibly counteracts the diabetogenic effects of immunosuppression or overrides the receptor defect occurring with insulin resistance. Thus, recipients with portally drained pancreases may have a tendency to ward slightly higher glucose levels. The long-term sequelae of this phenomenon remain to be determined. Only a few cases of recurrent insulinitis resulting in pancreatic graft failure have been described. Primary non-function of a pancreas graft is virtually nonexistent due to optimal donor quality.

For pancreas recipients with bladder-drained exocrine secretions, urinary amylase levels can be monitored.^{24–27} Studies have demonstrated that urinary amylase levels expressed in units per hour are more consistent compared with measurements in units per liter and lead to more accurate assessment of pancreas graft function. An analysis of a 12- or 24-hour urine collection in which urinary amylase levels have declined 50% or more from baseline is suggestive of rejection or pancreatitis. When confronted with this situation, further evaluation and probable biopsy are warranted either percutaneously via US or computed tomography (CT) guidance or transcystoscopically, assisted by US guidance.^{39–41} The de-

velopment of hematuria in bladder-drained pancreas recipients also warrants further evaluation and may necessitate the initiation of continuous bladder irrigation through a three-way Foley catheter to prevent obstructive thrombus formation. Cystoscopy is usually necessary to determine the etiology and/or remove the clot. Urethritis or cystitis due to enzymatic irritation, the most common cause of hematuria, may resolve with increased bicarbonate supplementation.⁴² Enteric conversion may be required for refractory irritation; however, such an extreme intervention is rarely required in the early postoperative period.⁴³ Bleeding from the duodenal-bladder anastomosis may arise, especially when a stapled anastomosis is performed. This complication can be avoided by oversewing the staple line at the time of the anastomosis. If a problem does develop, staples can be removed cystoscopically, although enteric conversion may ultimately be required to alleviate the bleeding.

Serum amylase and lipase levels provide additional means for following pancreas function, especially for enterically drained grafts.^{44,45} However, these markers lack the sensitivity and specificity of urinary amylase. Serum human anodal trypsinogen (HAT) has been shown to complement serum amylase and lipase levels in the determination of graft dysfunction.^{46,47} But, few laboratories are equipped to monitor this factor.

In the immediate postoperative period, serum amylase and lipase levels may be significantly elevated despite good glucose control and endocrine function. These early elevations usually result from reperfusion injury and resolve spontaneously. Some centers use somatostatin analogs to minimize the pancreatic inflammatory response.^{48–52} However, reports are only anecdotal and an absolute benefit remains to be shown. A few authors describe a beneficial effect when octreotide is administered at 100 mcg SQ every 8 hours. Use of this agent is in general reserved for the intraoperative findings of restrictive pancreatic edema, subcapsular hematoma, or profound duodenal edema.

Early rejection during the initial hospitalization appears to be decreasing in frequency as immunosuppressive regimens evolve.^{18–23} The sentinel sign of rejection in SPK recipients still remains a rise in serum creatinine. Following elimination of other possibilities for an abnormal creatinine level (dehydration, calcineurin toxicity, ureteral obstruction, bladder dysfunction, or vascular compromise), a percutaneous renal biopsy with US guidance is warranted. In some SPK recipients, serum amylase or lipase levels may rise while creatinine levels remain stable. In such situations, a transplant renal biopsy is still warranted, especially if an enteric-portal-drained pancreas is present.⁵³ Only in rare cases is a pancreas biopsy necessary to determine rejection if both the kidney and pancreas are from the same donor. It has been shown, however, that in an SPK recipient, one organ may have independent rejection while the other organ remains rejection free.^{54–57} For PTA and PAK recipients, the ability to follow rejection is somewhat more difficult. Thus, most centers are reluctant

to perform portal-enteric drainage for those procedures. Bladder-drained PTA and PAK recipients are ensured that all possible modalities to monitor pancreatic rejection are intact. Further, if serum or urinary amylase levels are suggestive of rejection the option of a transcystoscopic, transduodenal biopsy is still available should the pancreas not be approachable via US- or CT-guided percutaneous biopsy.

Antimicrobial Prophylaxis

Given their underlying disease state, diabetic patients pretransplant are inherently immunocompromised. Thus, prophylactic coverage against micro-organisms is paramount during the perioperative period. The literature clearly demonstrates that early infection results in the highest incidence of graft loss and in serious patient morbidity and mortality.^{58–61} Broad-spectrum agents covering gram-negative, gram-positive and anaerobic bacteria are recommended. Various single agents or combinations are available and should be given over the first 24 to 48 hours posttransplant. Recipients with positive urine cultures (from preoperative specimens) or positive intraoperative duodenal stump cultures should have antibiotic coverage for 3 to 7 days. Retrospective studies have demonstrated that pancreas recipients are at high risk for losing a second pancreatic allograft to the same infectious agent when their first graft was lost to infection. Even when a significant period has passed (months to years) between transplant procedures, infectious organisms can harbor in a dormant state and become active again following repeat surgical stress and the reintroduction of high-dose immunosuppression. Thus, a detailed microbial history of an individual transplant candidate is imperative so that appropriate antibiotic coverage can be initiated intraoperatively.

Due to the duodenal anastomosis in pancreas transplantation and the potential contamination of the operative field with small-bowel contents, many centers also recommend antifungal prophylaxis with fluconazole. Calcineurin inhibitor serum levels must be closely monitored when azoles are administered due to decreased metabolism of the immunosuppressant and resultant higher systemic concentrations. As demonstrated in several articles (referenced above), fungal infections result in the highest rates of graft loss and patient mortality.

Cytomegalovirus (CMV) prophylaxis is recommended for any positive combination of a donor–recipient pair.^{62,63} Controversy remains as to whether negative-to-negative combinations require prophylaxis. However, when antilymphocyte therapy is utilized CMV prophylaxis is almost always administered. As in KTA, early CMV infection in pancreas transplant recipients is hypothesized to result in increased MHC class 1 expression and increased risk of rejection. Gancyclovir and, more recently, valgancyclovir are at present the antiviral agents of choice in pancreas transplantation and can first be initiated intravenously or per nasogastric tube in the immediate postoperative period, and then orally when the pa-

tient tolerates a diet. Since the introduction of gancyclovir, combined with changes in approach to immunosuppression, overwhelming CMV infections resulting in ventilatory-dependent pneumonitis are virtually unheard of in the current practice of solid-organ transplantation. Patients intolerant to gancyclovir may tolerate valacyclovir, which provides adequate prophylaxis against CMV infection in renal only transplantation.⁶⁴ The val-preparation has increased absorptive properties compared to the parent compound. The efficacy of valgancyclovir in pancreas transplantation is at present under investigation. Dose adjustments must be made according to renal function for all of these antiviral preparations. Most centers begin sulfamethoxazole/trimethoprim immediately postoperatively and continue long-term prophylaxis against *Pneumocystis carinii* and noncardiac infections.

Stable Graft Function: Days 3 to 7

Patient hemodynamics usually stabilize by the close of the first 48 hours while graft function steadily improves. Following this phase of recovery, the recipient can be transferred to the transplant ward for less intense nursing care and monitoring. The use of incentive spirometry and pneumatic compression garments should be continued until the patient is fully ambulatory. The nasogastric tube placed intraoperatively can usually be removed when signs of bowel function have returned. However, in recipients with known histories of gastroparesis, or when there is concern regarding the adequacy of bowel function, early initiation of a motility agent such as metoclopramide is advised. Given the high incidence of autonomic neuropathy in this patient population, many recipients alternate between constipation and diarrhea during the early postoperative period. Thus, weeks may pass before bowel regularity occurs. With enteric drainage, upper gastrointestinal bleeding may occur as bowel function returns. Such hemorrhage usually results from the duodenal-jejunal anastomosis and should be self-limited. However, transfusion may be required; only rarely is surgical intervention required. Hemorrhage from the duodenojejunostomy can be avoided by diligent preparation of the enterotomies with completion of the anastomosis in a hemostatic, two-layer, hand-sewn fashion.

Timing of Foley catheter removal varies according to surgeon preference, usually within 1 to 3 weeks posttransplant. Again, communication between the surgeon and the rest of the transplant team is essential in this respect. As expected, recipients with thin bladder walls or tenuous anastomosis will probably benefit from longer decompression of the bladder. Similarly, recipients with known neurogenic bladders may need to wait until they are capable of self-catheterization prior to Foley removal. Patients with extremely small bladders may require a short period of "bladder training" prior to catheter removal. This process involves a serial increase in time increments during which the catheter is clamped. Typical pro-

ocols call for clamping for half-hour periods, steadily increasing to no more than 4 hours. The clamp is released as soon as the patient experiences a sensation of fullness or suprapubic pain. The training process may take 3 to 5 days and possibly more. For bladder-drained pancreas recipients, some centers routinely obtain a low-pressure cystogram prior to catheter removal to determine the presence of a bladder leak.⁶⁵ If the aforementioned study is indeterminate, an air-contrast CT cystogram may be warranted to fully evaluate any concerns prior to catheter removal.⁶⁶

The patient should be encouraged to be out of bed and ambulate no later than postoperative day three. For larger patients, an abdominal binder is recommended to aid in relieving abdominal wall strain and pressure.

Poor wound healing secondary to long-standing diabetes and immunosuppression is always a concern in this patient population. Daily observation of the abdominal incision for signs of infection or dehiscence is mandatory. Fascia is usually closed with a #1 nonabsorbable monofilament suture with the skin approximated with staples. Wound drainage usually requires removal of a few staples so that proper inspection and packing can be performed. For a noninfected wound, skin staples remain for 2 to 3 weeks prior to removal.

In most cases, oral intake can begin by postoperative day 4 or 5 and advance as tolerated. Conversion of all medications should begin once oral intake is clearly established. Over the course of the ensuing days, the recipient is encouraged to become more independent. Bladder-drained pancreas recipients may have difficulty with fluid consumption and acidosis due to loss of pancreatic secretions in the urine. Thus, some require placement of a tunneled central venous catheter prior to hospital discharge so that IV access is available for outpatient fluid and electrolyte replacement. Intensive instruction commences as early as possible regarding medications and follow-up care. The educational process should include a family member or friend who will be involved in the recipient's home care.

Most centers now boast that pancreas transplant recipients are discharged by the end of the first week—a vast change from a decade ago, when hospitalizations of a month or more were common. At the time of hospital discharge, a legible, accurate list of discharge medications (including dose, route, and frequency) and instructions should be sent home with the patient (Table 9.1.4). The patient should initially obtain laboratory studies three times a week. This schedule is then tapered to once a month by the end of 6 to 9 months as comfort with graft stability ensues. For patients having some difficulty dealing with the complexities of the transplant process, home health nursing and social work intervention should be arranged to assist the patient and their families during this transition period. Such assistance is usually required for 2 to 4 weeks after hospital discharge. If the patient lives a significant distance from the transplant center, temporary local lodging is recommended for about 2 weeks before returning home. Doing so eliminates repeat long-distance travel

TABLE 9.1.4. Template for routine discharge instructions.

1. Discharge to home
2. Return to clinic in 1–2 wk for follow-up care and staple removal
3. Labs: Q M–W–F CBC, BMP, serum amylase and lipase, prograf level, urinary amylase (bladder drained only)
Q 3–6 mo HgBA1c
3. No heavy lifting for 4–6 wk; wear binder when active
4. Keep wound clean and dry, notify MD for signs of infection
5. Urinate no greater than every 4 h while awake
6. Diet as tolerated
7. Daily blood pressure check (only for hypertensive history)
8. Medications
 - Immunosuppression (MMF, FK, and prednisone taper)
 - Nystatin s/s
 - H₂-blocker
 - CMV prophylactic agent
 - Sulfa/trim
 - BP medications
 - Stool softener
 - Others: Per history
9. Notify your primary physician of hospital discharge; schedule routine visit.
Notify transplant center if primary physician has not received hospital summary prior to visit.

M–W–F, Mon–Wed–Fri; s/s, swish/swallow.

and minimizes phone calls to the transplant center during this difficult period. Of utmost importance, communication with the referring and primary care physicians is imperative to maintain continuity of care.

Conclusions

Pancreas transplantation is a life-altering procedure that given its long-term goals is actually lifesaving. To achieve success in stabilizing the often deadly secondary complications of diabetes, prolonged function of a pancreatic allograft depends on a smooth, uncomplicated postoperative course. As addressed in this chapter, the complexity of the diabetic patient undergoing a pancreas transplant—whether SPK, PAK, or PTA—demands close attention to detail . . . a certain hypervigilance that is almost unprecedented. Many pitfalls can confront the transplant team and recipient in the early postoperative period. However, by carefully monitoring every aspect of the recovery phase most of the dangers can be avoided. The recipient can then successfully move on to the next phase of the transplant process: the long-term maintenance of allograft function.

References

1. Humar A, Kandaswamy R, Drangstveit MB, Parr E, Gruessner AG, Sutherland DE. Prolonged preservation increases surgical complications after pancreas transplants. *Surgery* 2000;27:545–551.
2. Tollema J, Tyden G, Brattstrom C, Groth CG. Anticoagulation therapy for prevention of pancreatic graft thrombosis: Benefits and risks. *Transplant Proc* 1988;20:479–480.
3. Troppman C, Gruessner AC, Dunn DL, Sutherland DE, Gruessner RW. Surgical complications requiring early relaparotomy after pancreas transplantation. A multivariate risk factor and economic impact analysis of the cyclosporine era. *Ann Surg* 1998;227:255.
4. Elkhmmas EA, Henry ML, Tesi RJ, Sommer BG, Ferguson RM. Control of metabolic acidosis after pancreas transplantation using acetazolamide. *Transplant Proc* 1991;23:1623–1624.
5. Peltenburg HG, Mutsaerts KJ, Hardy EL, van Hooff JP. Sodium lactate as an alternative to sodium bicarbonate in the management of metabolic acidosis after pancreas transplantation. *Transplantation* 1992;53:225–226.
6. Schang T, Timmermann W, Thiede A, Najarian JS, Sutherland DE. Detrimental effects of fluid and electrolyte loss from duodenum in bladder-drained pancreas transplants. *Transplant Proc* 1991;23:1617–1618.
7. Dafoe DC, Campbell DA Jr, Rosenberg L, et al. Does exogenous insulin infusion (islet “rest”) improve pancreas transplant endocrine function? *Transplant Proc* 1989;21:2827–2828.
8. Kaplan B, Wang Z, Abecassis MM, Fryer JP, Stuart FP, Kaufman DB. Frequency of hyperkalemia in recipients of simultaneous pancreas and kidney transplants with bladder drainage. *Transplantation* 1996;62:1174–1175.
9. England MR, Gordon G, Salem M, Chernow B. Magnesium administration and dysrhythmias after cardiac surgery. A placebo-controlled, double-blind, randomized trial. *JAMA* 1992;268:2395–2402.
10. Troppman C, Gruessner AC, Benedetti E, Papalois BE, Dunn DL, Najarian JS, Sutherland DER, Gruessner RW. Vascular graft thrombosis after pancreatic transplantation: Univariate and multivariate operative and non-operative risk factor analysis. *J Am Coll Surg* 1996;182:285–316.
11. Gruessner RWG, Sutherland DER. Simultaneous kidney and segmental pancreas transplants from living-related donors: The first two successful cases. *Transplantation* 1996;61:1265–1268.
12. Cicalese L, Rastellini C, Sileri P, Asolati M, Milenski S, Vasquez E, Benedetti E. Successful simultaneous pancreas–kidney transplantation from well-matched living related donors. *Transplantation* 2000;69:s213.
13. Spicer ST, Gruenewald S, O’Connell PJ, Chapman JR, Nankivell BJ. Low-dose dopamine after kidney transplantation: Assessment by Doppler ultrasound. *Clin Transplant* 1999;13:479–483.
14. Palmer BF, Dawidson I, Sagalowsky A, Sandor Z, Lu CY. Improved outcome of cadaveric renal transplantation due to calcium-channel blockers. *Transplantation* 1991;52:640.
15. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil: A review. *Am J Med* 1991;90:375.
16. Ferguson CJ, Hillis AN, Williams JD, Griffin PJ, Salaman JO. Calcium-channel blockers and other factors influencing delayed function in renal allografts. *Nephrol Dialysis Transplant* 1990;5:816.
17. Vander Schaff MR, Hene RJ, Floor M, Blankestijn PJ, Koomans HA. Hypertension after transplantation. Calcium-channel blocker or converting enzyme blockade? *Hypertension* 1995;25:77–81.
18. Kaufman DB, Burke G, Bruce D, Sutherland D, Johnson C, Gaber AO, Merion R, Schweitzer E, Marsh C, Alfrey E, Leone J, Concepcion W, Stegall M, Gores P, Danovitch G, Tolzman

- D, Scotellaro P, Salm K, Keller A, Fitzsimmons WE. The role of antibody induction in simultaneous pancreas kidney transplant patients receiving tacrolimus + mycophenolate mofetil immunosuppression. *Transplantation* 2000;69:s206.
19. Leone JP, Taylor RJ. Basiliximab induction versus no induction in simultaneous kidney pancreas transplantation using mycophenolate/tacrolimus/prednisone maintenance immunosuppression. *Transplantation* 2000;69:s410.
 20. Odorico J, Elkhammas E, Secchi A, Rigotti P, Somberg K, Di-rault D. A multicenter trial of simulect in combination with neoral, cellcept and steroids for the prevention of acute rejection in kidney-pancreas transplantation: A low rate of rejection without recurrent diabetes mellitus. *Transplantation* 2000;69:s409.
 21. Elkhammas E, Henry M, Demirag A, Carmona M, Bumgardner G, Pelletier R, Ferguson R. Basiliximab versus OKT3 in primary simultaneous pancreas-kidney transplant recipients. *Transplan-tation* 2000;69:s407.
 22. Stratta RJ, Alloway RR, Hodge E. An open-label, comparative trial of two daclizumab dosing strategies versus no antibody induction combined with tacrolimus, mycophenolate mofetil, and steroids for the prevention of acute rejection in simultaneous kidney/pancreas recipients: Interim analysis. *Transplantation* 2000; 69:s408.
 23. Willand AM, Fink JC, Philosphe B, Farney AC, Schweitzer EJ, Colonna JO, Weir MR, Bartlett ST. Experience with thy-moglobulin induction therapy in pancreas transplant recipients. *Transplantation* 2000;69:s408.
 24. Gruessner RWG, Sutherland DER. Clinical diagnosis of pan-creatic allograft rejection. In: Solez, Racusen, Billingham, eds. *Solid Organ Transplant Rejection*. New York: Dekker Inc; 1996:455-499.
 25. Prieto M, Sutherland DE, Fernandez-Cruz L, Heil J, Najarian JS. Urinary amylase monitoring for early diagnosis of pancreas al-lograft rejection in dogs. *J Surg Res* 1986;40:597-604.
 26. Prieto M, Sutherland DER, Fernandez-Cruz I, Heil J, Najarian JS. Experimental and clinical experience with urine amylase monitoring for early diagnosis of rejection in pancreas trans-plantation. *Transplantation* 1987;43:73-79.
 27. Powell CS, Lindsey NJ, Nolan MS, et al. Urinary amylase as a marker of rejection in duct to ureter drained pancreas grafts. *Transplant Proc* 1987;19:1023-1025.
 28. Bernard DR, Delanghe JR, Langlois MR. Difficulties in evalu-ating urinalysis following combined pancreas-kidney transplan-tation. *Ann Clin Biochem* 1997;34:664-667.
 29. Patel B, Markivee CR, Manhanta B, et al. Pancreatic transplan-tation: Scintigraphy, US, and CT. *Radiology* 1988;167:685-687.
 30. Letourneau JG, Maile CW, Sutherland DER, Feinberg SB. Ul-trasound and computed tomography in the evaluation of pan-creatic transplantation. *Rad Clin North Am* 1987;25:345-355.
 31. Letourneau JG. Sonography, CT, and MRI of pancreas allografts. In: Letourneau JG, Dayu DL, Ascher NL, eds. *Radiology of Or-gan Transplantation*. St. Louis, MO: Mosby-Yearbook; 1991: 257-266.
 32. Nghiem DD, Ludrosky L, Young JC. Evaluation of pancreatic circulation by duplex color Doppler flow sonography. *Transplant Proc* 1994;26:466.
 33. Moulton JS, Munda R, Weiss MA, Bubberg DJ. Pancreatic trans-plants: CT with clinical and pathologic correlation. *Radiology* 1989;38:27-29.
 34. Dachman AH, Newmark GM, Thistlethwaite JR, Oto A, Bruce DS, Newell KA. Imaging of pancreatic transplantation using por-tal venous and enteric exocrine drainage. *AJR* 1998;171:157-163.
 35. Yuh WTC, Hunsicker LG, Sato Y, et al. Application of mag-netic resonance imaging in pancreas transplantation. *Diabetes* 1989;38:27-29.
 36. Contis JC, O'Connor TP, Holland GA, et al. Noninvasive eval-uation of bladder-drained whole pancreaticoduodenal transplants with magnetic resonance angiography. *Transplant Proc* 1994;26: 464-465.
 37. Krebs TL, Daly L, Wong-You-Cheong JJ, Carroll K, Bartlett ST. Acute pancreatic transplant rejection: Evaluation with dynamic contrast-enhanced MR imaging compared with histopathologic analysis. *Radiology* 1999;210:437-442.
 38. Gruessner RWG, Burke GW, Stratta R, Sollinger HW, Benedetti E, Margh C, Stock P, Boudreaux JP, Martin M, Drangstveit MB, Sutherland DER, Gruessner A. A multicenter analysis of the first experience with FK 506 for induction and rescue therapy after pancreas transplantation. *Transplantation* 1996;61:261-273.
 39. Allen RDM, Wilson TG, Grierson JM, Greenberg ML, Earl MJ, Nankivel BJ, Pearl TA, Chapman JR. Percutaneous biopsy of bladder-drained pancreas transplants. *Transplantation* 1991;51: 1213-1216.
 40. Jones JW, Nakhleh RE, Casanova D, Sutherland DE, Gruessner RW. Cystoscopic transduodenal pancreas biopsy: A new needle. *Transplant Proc* 1994;26:527-528.
 41. Bennedetti E, Najarian JS, Sutherland DER, Gruessner AC, Nakhleh RE, Troppman C, Hakim NS, Pirenne J, Gruessner RW. Correlation between cystoscopic biopsy results and hyperamy-lasuria in bladder-drained pancreas transplants. *Surgery* 1995; 118:864-872.
 42. Sollinger HW, Messing EM, Eckhoff DE, Stegal MD, Pirsch JD, D'Alessandro AM, Kalayoglu MM, Knechtle SJ, Hickey D, Belzer FO. Urological complications in 210 consecutive simul-taneous pancreas-kidney transplants with bladder drainage. *Ann Surg* 1993;218:561-570.
 43. Sollinger HW, Sasaki TM, D'Alessandro AM, Knechtle SJ, Pirsch JD, Kalayoglu MM, Belzer FO. Indications for enteric conversion after pancreas transplantation with bladder drainage. *Surgery* 1992;112:842-846.
 44. Hesse UJ, Sutherland DE. Influence of serum amylase and plasma glucose levels in pancreas cadaver donors on graft func-tion in recipients. *Diabetes* 1989;38(suppl 1):1-3.
 45. Stratta RJ, Sollinger HW, Groshek M, et al. Differential diag-nosis of hyperamylasemia in pancreas allograft recipients. *Trans-plant Proc* 1990;22:675-677.
 46. Douzdjian V, Cooper JL, Abecassis MM, Corry RJ. Markers for pancreatic allograft rejection: Comparison of serum anodal trypsinogen, serum amylase, serum creatinine and urinary amy-lase. *Clin Transplant* 1994;8:79-82.
 47. Perkal M, Marks C, Lorber MI, Marks WH. A three-year expe-rience with serum anodal trypsinogen as a biochemical marker for rejection in pancreatic allografts. False positives, tissue biopsy, comparison with other markers, and diagnostic strate-gies. *Transplantation* 1992;53:415-419.
 48. Basadonna G, Fox U, Ribaldone G, et al. The use of SMS 201-995, a somatostatin analog, in pancreas transplantation. *Transplant Proc* 1990;22:602-603.

49. Chao SH, Chieng PU, Lee PH, Chu SH, Chen KM. Octreotide effects on pancreatic graft pancreatitis in inbred pigs. *Transplant Proc* 1996;28:1799–1801.
50. Nicholson CP, Barr D, Oeltjen MR et al. The effect of somatostatin 201–995 on the early course of porcine pancreaticoduodenal allotransplantation. *Transplant Proc* 1991;23:1587–1588.
51. Stratta RJ, Taylor RJ, Lowell JA, et al. Randomized trial of Sandostatin prophylaxis for preservation injury after pancreas transplantation. *Transplant Proc* 1993;25:3190–3192.
52. Stratta RJ, Taylor RJ, Lowell JA et al. Selective use of Sandostatin in vascularized pancreas transplantation. *Am J Surg* 1993;166:598–604.
53. Shapiro R, Jordan ML, Scantlebury VP, Vivas CA, Jain A, McCauley J, Egidi MF, Randhawa P, Chakrabarti P, Corry RJ. Renal allograft rejection with normal renal function in simultaneous kidney/pancreas recipients: does dissynchronous rejection really exist? *Transplantation* 2000;69:440–441.
54. Margreiter R, Klima G, Bomuller C, et al. Rejection of kidney and pancreas after pancreas–kidney transplantation. *Diabetes* 1989;38:79–81.
55. Dubernard JM, Traeger J, La Rocca E, et al. Experience of the Hopital Deouard Herriot, University of Lyon I, Lyon, France. In: Dubernard JM, Sutherland DER, eds. *International Handbook of Pancreas Transplantation* 1989. Dordrecht, The Netherlands: Kluwer, 1989:389–398.
56. Gruessner RWG, Najarian JS, Gruessner A, Sutherland DER. Comparison of rejection in clinical transplantation of pancreas alone or associated with kidney transplant. In: Touraine JL, Traeger J, Detuel H, et al., eds. *Transplantation and Clinical Immunology: Multiple Transplants*. vol. 22. Amsterdam: Excerpta Medica; 1991:47–54.
57. Tesi RJ, Henry ML, Elkhannas EA, et al. The frequency of rejection episodes with combined kidney–pancreas transplant—the impact on graft survival. *Transplantation* 1994;58:424–430.
58. Pirsch JD, Odorico JS, D'Alessandro AM, Knechtle SJ, Becker BN, Sollinger HW. Posttransplant infection in enteric versus bladder-drained simultaneous pancreas–kidney transplant recipients. *Transplantation* 1998;66:1746–1750.
59. Everett JE, Wahoff DC, Statz C, Gillingham KJ, Gruessner AC, Gruessner RWG, Gores PF, Sutherland DER, Dunn DL. Characterization and impact of wound infection after pancreas transplantation. *Arch Surg* 1994;129:1310–1317.
60. Benedetti E, Gruessner AC, Troppman C, Papalois BE, Sutherland DER, Dunn DL, Gruessner RWG. Intra-abdominal fungal infections after pancreatic transplantation: Incidence, treatment, and outcomes. *J Am Coll Surg* 1996;183:307–316.
61. Papalois BE, Troppmann C, Gruessner AC, Benedetti E, Sutherland DER, Gruessner RWG. Long-term peritoneal dialysis before transplantation and intra-abdominal infection after simultaneous pancreas–kidney transplantation. *Arch Surg* 1996;131:761–766.
62. Fishman JA, Rubin RH. Infection in the organ transplant recipient. *N Engl J Med* 1998;338:1741–1751.
63. Kaufman DB, Parker M, Leventhal J, Koffran A, Abecassis M, Fryer J, Stuart J, Stuart FP. Multivariate analysis of CMV in simultaneous pancreas–kidney transplantation in the mycophenolate mofetil/tacrolimus era. *Transplantation* 2000;69:s271.
64. Lowance D, Neumayer HH, Legendre CM, Squifflet JP, Kovarik J, Brennan PJ, Norman D, Mendez R, Keating MR, Coggon GL, Crisp A, Lee IC. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. *N Engl J Med* 1999;340:1462–1470.
65. Ciancio G, Burke G, Lynne C, et al. Urodynamic findings following bladder-drained simultaneous pancreas–kidney transplantation. *Transplant Proc* 1997;29:2912–2913.
66. Longley DG, Dunn DL, Gruessner R, Halvorsen RA, Sutherland DER, Letourneau JG. Detection of pancreatic fluid and urine leakage after pancreas transplantation: Value of CT and cystography. *AJR* 1990;155:997–1000.

9.2 Complicated Course

9.2.1 Imaging Studies and Interventional Radiology

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Imaging advances have paralleled the improvements in organ procurement, operative technique, immunosuppression, and antimicrobial prophylaxis to contribute to a dramatic increase in pancreas allograft survival. The clinical signs and symptoms of complications after a pancreas transplant are often nonspecific, so imaging plays an important role in providing an early diagnosis. With imaging guidance, safe and accurate biopsies can be readily accomplished; many complications can be successfully managed with a percutaneous approach.

Imaging Techniques and Normal Graft Appearance

Ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), angiography, and nuclear scintigraphy are the most important modalities currently used to study pancreas allografts. A transplanted pancreas is a difficult organ to image, frequently requiring more than one modality for a diagnosis. The pelvic location of the pancreas allograft when drained through the urinary bladder facilitates imaging, US in particular. Imaging can be considerably more difficult when grafts are placed higher in the pelvis or in the low abdomen, as is usual with enteric drainage.

US

Ultrasonography of pancreas allografts is optimally done with a 2.0- to 3.5-MHz transducer; the urinary bladder should be moderately distended. The normal sonographic texture of pancreas allografts consists of homogeneous medium-level echoes, similar to a healthy native pancreas (Fig 9.2.1.1). Even if the graft is normal, the margins may be difficult to define

because of the proximity of adjacent bowel loops and the lack of a discrete capsule. The pancreatic duct should not be greater than 2 to 3 mm in diameter. The identification of the graft may be improved by using color Doppler to identify the low-resistance arteries and veins within as well as outside the graft. The homogeneous perfusion of a healthy graft makes it easy to differentiate from surrounding structures, in particular when utilizing power Doppler.

CT

Computed tomography is performed after oral contrast to differentiate the graft parenchyma from nearby bowel loops. Intravenous (IV) contrast helps assess graft perfusion and can be critical in differentiating the graft from other soft tissues that may surround it. However, pancreas transplant recipients often have associated poor kidney function or other risk factors that limit the ability to use IV contrast. Another CT study that is frequently useful in recipients with bladder drainage is a CT-controlled cystogram; it is performed by injecting diluted contrast and air via a Foley catheter to delineate the duodenal stump and check for a leak.

The graft parenchyma enhances uniformly, similar to a healthy native pancreas (Fig 9.2.1.2). The graft is usually seen in the right iliac fossa, extending in a cephalad direction and parallel to the ascending colon. It should be well defined, with no edema or fluid in the surrounding soft tissues. Graft diameter may vary depending on the surgical technique. It is thicker if compressed in the pelvis.

Sequential studies will on occasion reveal changes in graft size and orientation.¹

The modern fast scanners allow thin (2 to 3 mm) collimation with overlapping reconstruction. Thus, arterial anatomy—especially the anastomosis and the branches leading up to the

A

B

FIGURE 9.2.1.1. (A) The homogeneous moderate echogenicity of the pancreas graft (thin arrows), seen here in a transverse section, clearly differentiates it from surrounding, slightly more hyperechoic, and possibly slightly inflamed fat (arrowheads). Fluid-filled loops of bowel can on occasion be difficult to differentiate from PPF collections. The vessels (fat arrow) have echogenic walls and can be easily differentiated from fluid collections with color Doppler. (B) In the longitudinal view, the pancreas graft (thin arrows) is superficial to the splenic vein (fat arrow). A short segment of the duct (arrowheads) is seen, with a somewhat atypically hyperechoic posterior wall (arrowheads).

graft—can be well demonstrated by CT angiography (CTA). Computed tomography angiography has a better spatial resolution than MR angiography (MRA) and so accurately diagnoses vascular problems such as critical stenosis, arteriovenous fistula (AVF), and vascular occlusion. Even though it is anatomically accurate, CTA is infrequently used for several reasons.

First, the contrast dose for CTA is high, commonly 125 to 150 cc. Because most pancreas transplant recipients also undergo a kidney transplant, the contrast dose becomes crucial. Second, CTA scan times for a single detector scanner can be so long that timing the scan to obtain optimal arterial phase images is difficult, even with automated contrast detection capabilities to initiate the scan. But, MRA scan times are short

enough that several acquisitions can be taken in a short time to document both arterial and venous phases of the examination. Third, MRI has better soft tissue contrast, allowing for a ready distinction between the graft and perigraft tissues; with the use of contrast, MRI is as accurate as CTA in assessing pancreas graft viability.

MRI

Multiplane imaging is easily performed with MRI. A variety of sequences allow evaluation of both anatomic and physiological parameters. A pancreas graft can often be seen in its entirety in coronal plane images. However, axial plane imaging helps to correlate results with those of CT. On T₁-

FIGURE 9.2.1.2. On contrast-enhanced CT, the pancreas graft (thin arrows) enhances uniformly; the vessels (arrowhead) have slightly greater density. Portions of the pancreas that do not uniformly enhance may represent areas that are acutely inflamed or necrotic (as is frequent with pancreatitis). Slight deformity of the adjacent psoas muscle and a small fluid collection, as seen on the anterior surface of the psoas, are a frequent and essentially normal finding when there are no associated symptoms or radiological signs of pathology.

weighted images (Fig 9.2.1.3A), a healthy graft is iso-intense to renal cortex. On T₂-weighted images (Fig 9.2.1.3B) the graft has intermediate signal intensity; in between muscle and fluid whereas any area of edema has high signal intensity and so can easily be differentiated from healthy portions of the graft.

Magnetic resonance angiography is currently performed using 3D-spoiled gradient echo sequences, with gadolinium enhancement.² Four- to five-volume sets, tailored to coincide with the arterial and venous phases of the examination, are obtained in a coronal plane. They are postprocessed at a workstation to generate volume-rendered images, maximum intensity projection (MIP) images, and multiplane reconstruction (MPR) images (Fig 9.2.1.4). Magnetic resonance angiography beautifully shows the vascular anastomosis and the vessels leading into and out of the graft. However, intra-pancreatic vessels are not well seen.

Angiography

Angiography is the gold standard for evaluating the graft arterial supply. The typical arterial supply consists of the visceral vessels that come with the graft and a large, bifurcated artery from the donor, which is used to reconstruct the arterial supply leading to the graft. The most commonly used “bifurcating vessel” is the donor common iliac artery (CIA); the hypogastric and external iliac artery (EIA) branches are used as an arterial Y-graft for reconstruction (see chapter 8.1.3). The donor hypogastric artery is anastomosed to the donor splenic artery and the EIA is anastomosed to the donor superior mesenteric artery (SMA). The final anastomosis is then made between the donor CIA and the recipient EIA.

Venous drainage is provided by the donor splenic vein,

which ends in a variable-length segment of the donor portal vein. The portal vein is then anastomosed to the recipient external iliac vein (EIV). The distal end of the donor splenic vein is ligated at the tail of the graft.

Angiography is initiated with nonselective injections in the EIA to confirm patency of the anastomosis and large vessels. To delineate the smaller intragraft vessels, selective injections are required. The venous phase of the examination is often delayed: Digital imaging for 20 to 25 seconds is often necessary.

Nuclear Scintigraphy

Scintigraphic studies are performed such that both perfusion (dynamic) and static images are obtained. Most commonly, we use a bolus injection of 20 mCi of ^{99m}technetium diethylenetriamine penta-acetic acid (DTPA) and obtain serial 2-second images for 60 seconds, followed by 500,000-count static images. A temporal and qualitative comparison of radioactivity is made between the graft and the adjacent iliac artery or aorta. The peak intensity in a normal graft typically occurs within 3 to 6 seconds after the peak iliac artery activity.²⁻⁴ The other radiopharmaceuticals that have been used are ⁷⁵Se-methionine, ^{99m}Tc sulfur colloid, ^{99m}Tc glucoheptonate, and ¹¹¹indium-labeled particles. In addition, ^{99m}Tc sestamibi has been shown to produce excellent-quality angiograms.⁵

Fluoroscopy

Fluoroscopic evaluation is infrequently used but can be a reasonably effective screening tool to identify a leak as a source of perigraft fluid. Contrast cystography is performed by opacifying the bladder with undiluted contrast, taking care to ensure that contrast refluxes into the duodenal segment (Fig

FIGURE 9.2.1.3. (A) The T_1 -weighted image of the healthy pancreas graft (thin arrows) reveals a signal intensity similar to that of the renal cortex. (B) The T_2 -weighted image helps to differentiate the pancreas graft (thin arrows) from adjacent tissues, especially fluid collections (which are extremely bright).

A

B

FIGURE 9.2.1.4. MRA allows clear definition of the entire pancreas graft (thin arrows) and determines that perfusion is present. An image such as this, taken when all of the arteries and larger veins are filled, permits accurate identification of the vessels entering and exiting the pancreas graft, including the splenic artery (fat arrow), adjacent splenic vein, SMA (small arrowhead), and the continuation of the splenic vein as the portal vein (large arrowhead) toward the iliac vein. Vessels are seen to the level of the first bifurcation, but intrapancreatic vessels are not accurately identified.

9.2.1.5). The two chains of surgical sutures are important landmarks that indicate the limits of the duodenal segment.

In pancreas transplant recipients who have undergone enteric conversion, fluoroscopic evaluation for a leak is more difficult; in fact, it is not possible if the drainage is into a

Roux-en-Y loop. Such recipients can only be evaluated if the transplant surgeon placed a small catheter into the afferent jejunum or terminal ileum near the anastomosis to the duodenal segment. If so, contrast can be carefully instilled into the jejunal or ileal loop to evaluate for an anastomotic leak.

FIGURE 9.2.1.5. The anastomosis between the bladder and duodenal segment (arrow) is usually fairly easy to identify. The end of the duodenal segment is on occasion visible because of the metallic surgical staple line (arrowhead).

Imaging Techniques and Complications of Pancreas Transplantation

Vascular Complications

Vascular complications are a significant cause of morbidity and a relatively common reason for pancreas graft removal. The overall incidence of vascular complications in a series published by Taylor et al.⁶ was 15.9%. Graft thrombosis, including both arterial and venous thrombosis, occurs in 5% to 14% of pancreas transplant recipients.⁷ A variety of other complications can also occur, including anastomotic bleed, arterial stenoses, perianastomotic pseudoaneurysms, and AVF.^{8,9}

Graft Vessel Thrombosis

Arterial and venous thrombosis is second only to rejection as a cause of pancreas graft failure.^{10,11} Venous thrombosis, which usually occurs in the first week posttransplant, is especially worrisome because of the risk of hemorrhagic pancreatitis, pancreatic necrosis, infection leading to sepsis, and thrombus propagation leading to deep vein thrombosis (DVT) and pulmonary embolism. In most cases, thrombosed grafts are not considered salvageable because parenchymal infarction occurs soon after thrombosis. Therefore, an early and accurate diagnosis is necessary to facilitate prompt graft excision and prevent further complications. The usual mechanism of early graft thrombosis in the first month posttransplant is either a technical error in fashioning one of the anastomoses or microvascular damage due to preservation injury. In most cases, late thrombosis results from autoimmune arteritis, in which gradual occlusion of the small blood vessels culminates in complete proximal occlusion of the vessels.^{12,13}

A pancreas transplant recipient with clinically suspected graft thrombosis should first be evaluated with color duplex sonography, preferably using a machine with power Doppler capabilities. Improved technical capabilities now permit precise visualization of the graft itself, as well as its arterial inflow and venous drainage in most cases. On B-mode sonography, the presence of graft inhomogeneity and peripancreatic fluid is evidence of graft injury. However, these findings are not diagnostic of thrombosis, as they may also be seen in rejection and pancreatitis. The sensitivity of US in diagnosing vascular thrombosis is 100%; specificity is 24%.¹⁴ The Doppler examination should include an evaluation of an artery and vein inside the graft parenchyma and also an artery and vein outside the graft, between the graft and the iliac vessels. The scan parameters must be optimized for small vessel slow flow detection; otherwise, the examiner may incorrectly diagnose vascular thrombosis.

A well-functioning graft should have low resistance (resistive index [RI] < 0.7) and arterial flow similar to a kidney graft artery.⁷ An elevated RI is a nonspecific finding seen in graft venous thrombosis, rejection, and other pathologic

processes. However, the RI values tend to be higher (>1) in thrombosis than in rejection: With no venous collaterals, obstruction to flow at the venous level represents an extreme degree of resistance to antegrade arterial flow. The absence of venous flow on the duplex exam is strongly suggestive of thrombosis. However, nonvisualization of the veins may also be due to extremely slow flow or other technical reasons rather than actual absence of flow. In a study by Foshager et al.,⁷ 9 of 11 patients with venous thrombosis had an RI > 1; only 2 of 43 control patients had an RI > 1. All 11 patients had absence of venous flow. Thus, this combination of findings (RI > 1 and absence of venous flow) is both sensitive and specific in diagnosing venous thrombosis.

On the duplex examination, the absence of arterial flow in all portions of the Y-graft (including the SMA and splenic artery) is the only reliable evidence of arterial thrombosis. If a definite diagnosis cannot be made, other imaging modalities can be used.

The multiphasic breath-hold gadolinium-enhanced 3D MRA is now emerging as an extremely useful tool in diagnosing vascular thrombosis, especially when the graft is poorly visible on US or when there is any suspicion of vascular thrombosis on duplex examination.^{2,15}

Absence of flow on MRI can be seen with acute vascular thrombosis, but it is not specific for that diagnosis. It can also be seen in cases without thrombosis but with extremely sluggish or to-and-fro flow due to severe graft injury, in particular chronic rejection. The sensitivity of MRA in detecting absence of flow is 100%; specificity is 93%.¹⁵

In the arterial phase of imaging the Y-graft, the SMA and splenic artery are assessed for patency. A low intravascular signal is suggestive of partial occlusion and no signal of total occlusion. In the venous phase of the MRA, nonopacification of vessels because of thrombosis is seen as serpentine signal voids within the graft parenchyma. The common sites of involvement are the SMV in the head of the pancreas, the splenic vein on the superior surface of the pancreatic body and tail, and the anastomotic site between the donor portal vein and recipient EIV. Other venous problems can also be identified on later images, such as slow flow because of a severely narrowed venous anastomosis.²

Lack of enhancement of graft parenchyma suggests infarction and necrosis and is an indication for pancreatectomy. Systemic anticoagulation for graft salvage has been successful when graft enhancement was noted on the MRI in the presence of venous thrombosis.^{2,16}

Nuclear scintigraphy has been used as a noninvasive screening test to assess graft perfusion, although false positive results do occur. A normal ^{99m}Tc DTPA or MAG3 flow study, in which the pancreas graft and iliac vessels are visualized on the same image, can rule out vascular thrombosis or occlusion. In a study of 78 pancreas transplant recipients by Snider et al.,¹⁴ the sensitivity was 93%; specificity was 64%. Partial or incomplete graft thrombosis is associated with an increase in time to peak signal in the graft, as compared

with the aortoiliac vessels, a decrease in uptake, and poor graft visualization. However, graft rejection with impending thrombosis also shows similar findings.

AVF and Pseudoaneurysm

Arteriovenous fistula and pseudoaneurysm are rare complications after a pancreas transplant. Causes include mycotic aneurysm, anastomotic leak, and needle biopsy. The morbidity and mortality associated with an untreated AVF or pseudoaneurysm is high. Surgery to treat these lesions, which are usually embedded in the graft parenchyma, can be difficult and result in graft loss. These lesions are often clinically silent or cause only subtle laboratory alterations. Unless they result in bleeding, they may escape diagnosis for long periods. Ultrasonography is an appropriate initial test when an AVF or pseudoaneurysm is suspected because it is highly sensitive in detecting both abnormalities. Computed tomography

angiography and MRA (Fig 9.2.1.6) are also highly sensitive in detecting vascular complications. However, angiography remains the most accurate study. The arteriogram is used to confirm or rule out the diagnosis and is also important for planning therapy.

In the management of AVF and pseudoaneurysm, percutaneous endovascular techniques have emerged as the preferred approach. Embolization of a pseudoaneurysm can be difficult. The large size and the weak wall preclude embolization of the sac (Fig 9.2.1.7A). If the vessel can be sacrificed, coil embolization of the artery both proximal and distal to the neck of the pseudoaneurysm is curative (Figs 9.2.1.7B and 9.2.1.7C). If the vessel cannot be sacrificed, the aneurysm can be excluded from the vessel lumen by placing a covered stent across its neck.

Percutaneous management of an AVF is usually possible using coils and balloons (Fig 9.2.1.8). Fortunately, most fistulae are between peripheral vessels; the fistula and the feeding artery are embolized simultaneously. If the fistula is more central, embolization is usually performed by advancing a catheter to the site of the fistula itself, and then gently pushing the coils in the small space between the artery and vein. If the fistula channel is long enough, multiple coils can be placed in a nest, which more securely closes the fistula.

Detachable balloons can also be used to occlude the fistula flow; they have the distinct advantages of being flow directed and repositionable. Mounted onto the end of a coaxial microcatheter, these small latex balloons are inflated at the desired site, checked with an angiogram, and then detached from the catheter. Coil and balloon embolization techniques do have several major limitations that can severely limit the ability to treat an AVF percutaneously. High flow through the fistula can prevent safe deployment of coils or balloons, resulting in an inadvertent pulmonary embolus. The length of the fistula, or of the vessel proximal to the fistula, may not be sufficient for device deployment. The portion of the graft supplied by the vessel may be relatively large or the collateral supply may be inadequate. The distal vein may thrombose if flow suddenly or severely decreases and if a portion of a coil or balloon partially obstructs the lumen.

Nonvascular Complications

Fluid Collection

Postoperative peripancreatic fluid collection (PFC) is a common finding on imaging studies after a pancreas transplant. The development of PFC increases the likelihood of graft dysfunction, graft loss, and recipient morbidity. In a series from the University of Nebraska, of 124 pancreas transplant recipients 24% (30) developed 80 symptomatic fluid collections that required intervention.¹⁷

All pancreas grafts are placed in an intraperitoneal location. In addition, however, a limited amount of extraperitoneal dissection is required during graft placement to establish

FIGURE 9.2.1.6. Reconstructed views from an MRA clearly show a large artery (thin arrow) entering the region of the AVF, with a large vein (fat arrow) draining into the iliac vein. The small and slightly tortuous splenic artery and vein are seen going in a cephalad direction. The fistula, therefore, is between the SMA and vein. The common venous trunk, the portal vein, can be seen crossing over the iliac artery to reach the iliac vein.

A **B** **C**

FIGURE 9.2.1.7. (A) The pseudoaneurysm (arrow) is weak walled and irregular, making coil embolization of the sac problematic. In cases such as this, the neck is often wide, further complicating any possible attempt to embolize the pseudoaneurysm itself. Fluid surrounds the pseudoaneurysm, which is likely a mixture of blood and edema. (B) The angiogram began with an injection in the iliac artery adjacent to the anastomosis. The pseudoaneurysm appears to arise from the upper of the two vessels, likely either the superior mesenteric artery or the anastomosis between the bifurcated vascular graft and SMA (thin arrow). The flow into the pseudoa-

neurysm is so low resistance that there is almost no antegrade flow into the adjacent splenic artery (fat arrow). (C) A small coil has been successfully lodged into the tiny segment of vessel leading into the pseudoaneurysm (thin arrow). A faint amount of contrast is seen entering the pseudoaneurysm, which later stopped. The partially subtracted outline of two coils that did not lodge in the neck but "popped" into the pseudoaneurysm can be seen in its right lateral recesses. With the flow into the pseudoaneurysm stopped, there is much better filling of the branches of the splenic artery (fat arrow).

A **B** **C** **D**

FIGURE 9.2.1.8. (A) A 3D reconstruction of the MRA nicely demonstrates the AVF in the tail region of the pancreas, likely between the splenic artery (thin arrow) and vein (fat arrow). The vessels probably have some small branches to normal parenchyma, but extend for a long enough distance toward the periphery of the graft that direct embolization of the artery feeding the AVF with coils was felt to be possible and acceptable. (B) Injection into the bifurcated conduit shows rapid flow into the splenic artery (thin arrow), which confirms the anatomy as seen on MRA and also fails to show any significant parenchymal branches arising from the artery near the fistula.

Given the rapid, low-resistance flow through the fistula, no flow is seen into any of the parenchymal arteries. This steal phenomenon is felt to be responsible for the signs of “graft failure” that frequently accompany an AVF. (C) Even a more peripheral injection into the splenic artery (thin arrow) fails to show anything but rapid flow into the splenic vein (fat arrow) and iliac vein. (D) After coil embolization of the distal splenic artery, the parenchymal vessels that arise from it can finally be identified. Embolization closer to the fistula itself was not done for fear of dislodging the coils into the venous circuit through the dilated vessels near the fistula.

exocrine drainage to the bladder and create the vascular anastomoses. Thus, PFCs after a pancreas transplant usually occur in an intraperitoneal location but can also be extraperitoneal.

The clinical presentation of a symptomatic PFC often includes fever, lower-abdominal pain, ileus, and hyperamylasemia. Less common symptoms include tachycardia, hypotension, graft tenderness, and anemia. The common causes of a symptomatic PFC include pancreatic phlegmon, pancreatic fistula, abscess, duodenal segment leak, hematoma, lymphocele, and urinoma (Figs 9.2.1.9, 9.2.1.10A, and 9.2.1.10B). Ultrasonography is a useful screening test to initially diagnose a PFC. However, CT is more accurate in characterizing the fluid and determining its true extent because the view is not limited by bowel gas. Computed tomography is also the preferred modality for therapeutic drainage of a PFC (Fig 9.2.1.10C).

Although CT and US are sensitive in detecting a PFC, both produce few distinct findings that can help determine the nature of the fluid collection. Gas around the graft on CT is common in the immediate postoperative period. However, the sudden appearance in a PFC of gas, or a progressive increase in its amount, most likely indicates an abscess. Gas in a PFC that contains high attenuation material, in particular in proximity to a vascular anastomosis, may represent nitrogen in a hematoma. In addition, an enhancing irregular rim increases the likelihood that a PFC is an abscess. Ultrasonography can be used to characterize the collection. It is much more accurate than CT in delineating debris or septa in a multiloculated fluid collection. Both debris and septa influence the techniques for approaching the lesion and the prognosis of percutaneous drainage. Precise characterization requires aspiration of diagnostic material for both chemical and

microbiologic analysis. High PFC amylase levels may suggest a pseudocyst or pancreatic ascites. High PFC amylase levels coupled with high PFC creatinine levels in bladder-drained transplants suggest an anastomotic or duodenal stump leak.

Leaks from a duodenoneocystostomy or the bladder occur with transplants that used bladder drainage for the exocrine secretions. Leaks from the duodenum or bladder occur in 9% to 14% of pancreas transplant recipients.^{18,19} It is believed that leaks within 4 weeks posttransplant are more likely to occur at the anastomosis between the bladder and duodenum. Leaks occurring after 4 weeks may be from the duodenal stump or from a perforated duodenal ulcer.²⁰

Plain CT is not usually helpful in diagnosing leaks because fluid or miscellaneous soft-tissue densities adjacent to the graft or the anastomosis between the duodenum and bladder are common in recipients without leaks and are therefore non-specific findings.¹⁸ However, an enlarging fluid collection on two sequential scans is strongly suggestive of a leak.

Fluoroscopic cystography or CT cystography is an accurate method to detect a leak. Bischof et al.¹⁹ first reported the technique that is currently in most widespread use for CT cystography, in which the bladder is filled with both contrast and air (Fig 9.2.1.11). This dual-contrast approach increases both the sensitivity and specificity of CT cystography. Computed tomography accurately detects both contrast media. Leaks can occur on either the anterior or posterior surfaces. In Bischof's study of 18 patients, the sensitivity was 92%; specificity was 100%. Pre- and postvoid scans were done to look for extravascular air or contrast as an indicator of a leak. In four patients, the leak could only be diagnosed on the postvoid scans.

Fluoroscopic cystography is only effective in identifying a leak if the leak can be seen with iodinated contrast injection;

FIGURE 9.2.1.9. The fluid collection (thin arrow) is clearly seen adjacent to the inhomogeneous, irregular, inflamed-appearing pancreas graft (fat arrows). Areas in the middle of the pancreas graft that do not enhance at all may be necrotic.

FIGURE 9.2.1.10. (A) Occasional fluid collections (thin arrows medially and laterally) can dissect relatively far from the pancreas graft into adjacent healthy tissues. When the pancreas graft is not obviously inflamed (as it is in this case), the fluid may represent hematomas, seromas, lymphoceles, or pseudocysts. (B) Large inhomogeneous fluid collections around the weakly enhancing pancreas graft (thin arrow) are often associated with fevers. Aspiration or percutaneous drainage is often the only way to make an accurate diagnosis and also offers a way to potentially cure the problem. (C) Percutaneous drainage is easily accomplished with CT fluoroscopy and “real-time” visualization of the needle tip. US drainage would surely have been possible in a case such as this, but differentiating inflammatory mass from tissue (including the pancreas graft itself) can be difficult with extensive inflammation.

A

B

C

FIGURE 9.2.1.11. On CT, it is easy to accurately visualize the anastomosis between the bladder and duodenum (arrow). Air, an excellent CT contrast agent, permits clear definition of an intact anterior bladder wall.

an air-contrast leak is essentially undetectable. Any contrast material extending beyond the metallic sutures that define the anastomosis and also serve as indicators of the limits of the duodenal segment is presumed to be a leak. Care should be taken when instilling contrast into the bladder, especially in the immediate postoperative period, to ensure that the bladder and duodenal segment are not overdistended. If they are, they could leak through or even disrupt the suture lines.

Optimal management of a PFC depends on early characterization and early treatment of the fluid, thereby decreasing morbidity and improving graft survival. Aspiration with biochemical and microbiologic assessment is the mainstay for characterization. Computed tomography, with or without CT fluoroscopy, is the most common imaging modality for guidance of aspiration and drainage. Larger or more superficial fluid collections are also readily amenable to US-guided techniques.

Aspiration is usually accomplished with 20- or 22-gauge needles, although 18- or 20-gauge needles may be required for higher viscosity fluids. In a high percentage of pancreas transplant recipients, percutaneous drainage catheter placement is technically successful. Complete therapeutic success with percutaneous drainage alone is less common. In a University of Minnesota study^{21,22} of 26 grafts with 38 catheter drains, complete and lasting therapeutic success was achieved in 35% (9) and temporary therapeutic success in 38% (10); percutaneous drainage failed in 27% (7). This low success rate was likely related to the recipients' immunocompromised condition, the presence of surgical foreign bodies, and the persistent leakage of pancreatic enzymes. The results did not appear to be related to the amylase level in the PFC or to associated bacterial or fungal infection. Percutaneous drainage of

the PFC was completely successful in all recipients who had undergone a posttransplant pancreatectomy.

Pancreatitis

The hallmark of pancreas graft injury from any source is pancreatitis. In the immediate postoperative period, the most common causes are acute rejection, preservation or reperfusion injury, or technical problems, in particular as they affect ductal integrity or vascular patency. Pancreatitis due to rejection is treated by intensifying antirejection agents. Reperfusion pancreatitis is self-limiting, usually resolving within several days. Reflux-induced pancreatitis is treated with urethral catheterization.

Most recipients in the immediate posttransplant period show signs of mild pancreatitis on imaging. Signs include graft enlargement, a thin rim of peritransplant fluid, and minimal infiltration of peripancreatic fat (Figs 9.2.1.12A and 9.2.1.12B). After the immediate postoperative period, pancreatitis may be suspected because of abdominal pain or elevated serum amylase levels.

With graft injury, pancreatic enzymes seep from the graft and cause severe inflammatory changes. Computed tomography is useful in assessing pancreatic necrosis, infarction, and pseudocyst formation. Findings are similar to what would be expected in native pancreas inflammation, including infiltration of peripancreatic fat, ascites, abnormal enhancement of pancreatic parenchyma, and intra- or extrapancreatic loculated fluid collections consistent with pseudocysts. Graft enlargement is difficult to appreciate without a baseline study.

Pancreatitis in extraperitoneal grafts can result in extensive necrosis of flank and lower-extremity musculature, which is

FIGURE 9.2.1.12. (A) On US, the signs of pancreatitis, which most commonly occurs immediately posttransplant, include an increase in graft size, haziness of the graft margins (thin arrows), and inhomogeneity of the parenchyma of the graft. In this image, an echogenic region is just posterior to the pancreas graft (fat arrow), representing air in an adjacent bowel loop and not air in an abscess. (This can be difficult to differentiate.) (B) CT is an accurate method to diagnose pancreatitis. Frequent signs include irregular enhancement of the pancreas graft, peri-pancreatic edema (which frequently appears to be a simple fluid on CT but on US is almost always a complex, mixed mass of echogenicity), and areas of stranding or infiltration of peripancreatic fat (arrow).

A

B

why the extraperitoneal site is no longer preferred. Extension of the phlegmonous process or pseudocysts into close proximity to the iliac vasculature must be viewed with concern: It may predispose to pseudoaneurysm formation and eventual erosion with catastrophic results.

Rejection

Rejection is by far the most common cause of graft failure.²³ Early detection of acute rejection is important for prompt initiation of antirejection therapy. Imaging findings have only

been minimally successful in detecting or predicting rejection. On US, graft enlargement and inhomogeneity may be seen, presumably because of edema or cellular infiltrate. Increased echogenicity, with or without an associated decrease in graft size, indicates chronic rejection. On US, an elevated RI has been found to correlate with rejection. In a University of Minnesota study,²⁴ the RI was compared with the type and degree of rejection in 17 recipients. The nine who had no rejection had a mean RI of 0.64 (range, 0.49 to 0.80). The six who had acute mild to moderate rejection had a mean RI of 0.67 (range, 0.56 to 0.73). The two who had acute severe rejection had a mean

RI of 0.85 (range, 0.80 to 0.90). Thus, the RI does not differentiate between acute mild to moderate rejection and absence of rejection. However, an elevated RI may be a sensitive indicator of acute severe rejection. Computed tomography of a graft with rejection may show nonspecific edema and heterogeneity in attenuation. The main role of CT in cases of possible rejection is in guiding percutaneous biopsy of the graft.

Magnetic resonance imaging appears to be emerging as a promising tool in detecting rejection. Earlier studies used unenhanced spin echo imaging techniques to detect graft edema, which is commonly associated with rejection. Edema is quantitatively identified when the glandular signal intensity is either less than that of muscle on T₁-weighted images or greater than or equal to the signal intensity of the bladder urine on T₂-weighted images. Recently, Krebs et al.²⁵ compared parenchymal enhancement on dynamic contrast-enhanced MR with histopathologic findings on biopsies. Grafts with rejection had a significant decrease in enhancement with gadolinium as compared with healthy grafts. Using a mean percentage of parenchymal enhancement, they calculated a sensitivity of 96% in diagnosing rejection.

With noninvasive techniques remaining largely nonspecific in diagnosing rejection, percutaneous image-guided biopsy has emerged as the method of choice. It offers an accurate diagnosis with reasonable safety. In two large series, the accuracy was 83% to 90%, the rate of major complications was 0% to 3%, and the rate of minor complications was 2% to 7%.^{26,27}

Computed tomography is the most accurate method to visualize the graft and its relationship to surrounding structures and is, therefore, the guiding technique of choice. Oral contrast is given to delineate the bowel. At the University of Minnesota, we perform the biopsy with a coaxial needle and an automated core biopsy needle. We biopsy the most accessible portion of the pancreas. We almost always use an active contrast enhancement technique. The outer guiding needle is positioned close to the graft and short of any graft-related vascular structures. The contrast is injected. Under CT fluoroscopy, the needle is advanced forward, avoiding any enhancing vessel. If CT fluoroscopy is not available, then a few axial CT sections are taken during contrast administration to rule out a vessel. We also routinely use gelfoam plugs postbiopsy to occlude the biopsy track; doing so decreases the postbiopsy compression time, the immobilization or bedrest time, and the size and incidence of hematomas on the immediate postbiopsy scan. If severe bleeding occurs after a biopsy, multiple gelfoam plugs (in some cases five or six) can be placed in the biopsy tract until bleeding totally ceases. The major complications of biopsy include hemorrhage and pancreatitis. Minor complications include a transient rise in serum amylase levels, mild hematuria, small hematomas, pain, and pseudocyst formation.

Urologic Complications

Almost all pancreas transplant recipients with bladder drainage develop some degree of postoperative hematuria.

Delayed hematuria is usually caused by duodenal ulceration; calculi and bladder tumors are less common causes. These problems are usually diagnosed cystoscopically. Imaging has no role to play except in detecting calculi or tumors.

Recurrent urinary tract infection (UTI) occurs in 10% of pancreas transplant recipients.²⁰ Imaging of UTI is limited to identifying complications and predisposing factors, such as calcification, diverticula, or a large postvoid residual. Urethritis and urethral stricture, which occur in about 3% of recipients, are best studied by a retrograde contrast urethrogram or urethroscopy. Inflammation of the bladder or duodenal segment can occur because of irritation by the exocrine pancreatic secretions. On cystography, this condition is seen as thickened folds and spasm, manifested by difficulty in distending the duodenal segment or bladder. If cystitis, inflammation of the duodenal segment, or urethral damage is too severe, the transplant surgeon may convert such recipients to enteric drainage.

Conclusions

Ultrasonography with Doppler is usually the initial modality employed to evaluate patients with suspected fluid collections and vascular complications.

Computed tomography is the most accurate method of diagnosing fluid collections, anastomotic leaks, and pancreatitis, especially in obese pancreas transplant recipients. At the University of Minnesota, it is the preferred method for guiding biopsies. It is even faster, more accurate, and safer when using CT fluoroscopy with active contrast enhancement.

Magnetic resonance imaging is increasingly used for the noninvasive evaluation of vascular complications, especially when Doppler is nondiagnostic. Its role in diagnosing rejection is promising.

Nuclear medicine studies can rule out a diagnosis of infarction. However, because of low specificity, they are not as often used as US or MRI. Their role will likely expand markedly as molecular imaging probes are developed that can evaluate specific questions about graft function, inflammation, and rejection.

Angiography is the gold standard for evaluating vascular complications; however, it is used only when vascular intervention is planned.

References

1. Schaapherder AF, de Roos A, Shaw PC, et al. The role of early baseline computed tomography in the interpretation of morphological changes after kidney pancreas transplantation. *Transplant Int* 1993;6(5):270-276.
2. Eubank WB, Schnuedk UP, Levy AE, et al. Venous thrombosis and occlusion after pancreas transplantation: Evaluation with breath hold gadolinium enhanced three dimensional MR imaging. *AJR* 2000;175:381-385.

3. Yuh WTC, Wiese JA, Abu-Yousef MM, et al. Pancreas transplant imaging. *Radiology* 1988;167:679–683.
4. Yuh WTC, Hawes DR, Abu-Yousef MM, et al. Pancreas transplant imaging. In: Freeney PC, Stevenson GW, eds. *Margulis & Burhenne's Alimentary Tract Radiology*. vol. 2, 5th ed. St. Louis, MO: Mosby Yearbook; 1994:1197–1191.
5. Sebastian A, Cuenca A, Li SF, et al. Pancreas transplant graft evaluation using the MIBI scan—a useful tool. *Transplant Proc* 1998;30:257–260.
6. Taylor RJ, Stevenson B, Stratta RJ, et al. Kidney pancreas transplantation: A review of the current status. *Urol Clin North Am* 1994;21:343–354.
7. Foshager MC, Hedlund J, Troppman C, et al. Venous thrombosis of pancreatic transplants: Diagnosis by duplex sonography. *AJR* 1997;169:1269–1273.
8. Lowell JA, Bynon JS, Stratta RJ, et al. Superior mesenteric arteriovenous fistula in vascularized whole organ pancreatic allografts. *Surg Gynecol Obstet* 1993;177:254–258.
9. Grenier N, Rousseau H, Douws C, et al. External iliac vein stenosis after segmental pancreas transplantation: Treatment by percutaneous endoprosthesis. *Cardio Vasc Intervent Radiol* 1993;16:186–188.
10. Gruessner A, Sutherland DER. Pancreas transplant results in the United Network for Organ Sharing (UNOS) United States of America registry compared with non-USA data in the international registry. In: Terasaki P, Cecka M, eds. *Clinical Transplants*. Los Angeles: UCLA Tissue Typing Laboratory; 1994:47–68.
11. Hanto DW, Sutherland DER. Pancreas transplantation: Clinical considerations. *Radiol Clin North Am* 1987;25:333–343.
12. Doujdian V, Abecassis MM, Cooper JL, et al. Pancreas transplant salvage after acute venous thrombosis. *Transplantation* 1993;56:222–223.
13. Nakhleh RE, Gruessner RW, Swanson PE, et al. Pancreas transplant pathology: A morphologic, immuno-histochemical, and electron microscopic comparison of allogeneic grafts with rejection syngeneic grafts and chronic pancreatitis. *Am J Surg Pathol* 1991;15:246–256.
14. Snider JF, Hunter DW, Kuni CC, et al. Pancreatic transplantation: Radiological evaluation of vascular complications. *Radiology* 1991;178:749–753.
15. Krebs TL, Daly B, Wong JJ, et al. Vascular complications of pancreatic transplantation: MR evaluation. *Radiology* 1995;196:793–798.
16. Fisher RA, Munda R, Madden R, et al. Pancreas transplant functional salvage after segmental venous thrombosis. *Transplant Proc* 1993;25(2):2138–2140.
17. Esterl RM Jr, Stratta RJ, Taylor RJ, et al. Diagnosis and treatment of symptomatic peripancreatic fluid collections after pancreas transplant. *Transplantation Proc* 1995;27(6):3057–3058.
18. Longley DG, Dunn DL, Gruessner R, et al. Detection of pancreatic fluid and urine leak after pancreas transplantation: Value of CT and cystography. *AJR* 1990;155:997–1000.
19. Bischof TP, Thoeni RF, Melzer JS. Diagnosis of duodenal leaks from kidney–pancreas transplants in patients with duodenovesical anastomoses: Value of CT cystography. *AJR* 1995;165:349–354.
20. Pazniak MA, Propeck PA, Kelcz F, et al. Imaging of pancreas transplants. *Radiol Clin North Am* 1995;33:581–594.
21. Letourneau JG, Hunter DW, Crass JR, et al. Percutaneous aspiration and drainage of abdominal fluid collections after pancreas transplantation. *AJR* 1988;150:805–809.
22. Letourneau JG. Sonography, CT, MRI of pancreas allografts. In: Letourneau JG, Day DL, Ashar NL, eds. *Radiology in Organ Transplantation*. St. Louis, MO: Mosby Yearbook; 1990.
23. Stratta RJ, Sollinger HW, Oerkman SB, et al. Early detection of rejection in pancreas transplantation. *Diabetes* 1989;38:63–67.
24. Aideyan OA, Foshager MC, Benedetti E, et al. Correlation of the arterial RI in pancreas transplantation of patient with transplant rejection. *AJR* 1997;168:1445–1447.
25. Krebs TL, Daly B, Wong JJ, et al. Acute pancreatic transplant rejection: Evaluation with dynamic contrast enhanced MR imaging compared with histopathologic analysis. *Radiology* 1999;210:437–442.
26. Aideyan OA, Schimdt AJ, Trenkner SW, et al. CT-guided percutaneous biopsy of pancreas transplants. *Radiology* 1996;201:825–828.
27. Lee BC, McGahan JP, Perez RV, et al. The role of percutaneous biopsy in detection of pancreatic transplant rejection. *Clin Transplant* 2000;14:493–498.

9.2.2 Surgical Complications

Christoph Troppmann

Despite a large potential recipient pool, widespread application of pancreas transplants has been hampered by substantial graft failures caused by surgical complications.^{1–9} In fact, the history of pancreas transplants, unlike that of other abdominal organ transplants, has largely been shaped by the associated complications. Surgical complications are so relevant because they frequently result in graft loss (e.g., from vascular graft thrombosis and intra-abdominal infection).^{6–8,10} Moreover, they increase recipient mortality significantly and augment transplant costs considerably.^{8,10} From 1983 through 1987, 25% of all pancreas grafts worldwide were lost from surgical complications (technical failures).¹ But, over the past decade and a half complication rates have dramatically decreased (Fig 9.2.2.1). From 1999 through 2001, only 7.3% of all primary pancreas grafts in the United States were lost from surgical complications¹¹; less than half of the technical failure rate even as compared with the 1987 through 1992 US cases.¹¹

Currently, graft thrombosis remains by far the most common technical failure, accounting for more than 70% of all graft losses from surgical complications in each of the three pancreas recipient categories (simultaneous pancreas and kidney [SPK], pancreas after kidney [PAK], and pancreas transplants alone [PTA]).¹¹ Ironical also, even though the islet cells account for less than 2% of the overall pancreas graft mass, all surgical complications after pancreas transplants result from the remaining 98% of the tissue transplanted with the islets (i.e., vasculature, exocrine parenchyma, and, for whole-organ pancreas grafts, the duodenum).¹²

A closer look at the history of the surgical complications after pancreas transplants demonstrates their impact on the evolution of the field. For physiological and technical reasons, most of the early pancreas grafts were enterically drained.^{13,14} However, intraperitoneal infections and anastomotic leaks, two of the most frequent complications, were as-

sociated with prohibitive morbidity and mortality.^{5,13,14} During those early years, immunosuppression was relatively nonspecific and mostly included potent polyclonal anti-T-cell antibodies, steroids, and azathioprine.

By the early 1970s, drainage of the exocrine pancreatic secretions into the urinary tract was seen as a means to prevent those often catastrophic complications.¹⁵ However, initial attempts at draining segmental pancreas grafts into the native ureter were also fraught with high rates of leakage, morbidity, and mortality.¹⁵ Short- and long-term results with duct-injected grafts were also suboptimal because of pancreatitis, pancreatic fistulas, and fibrosis.^{2,3,16} Hence, during the early 1980s safer alternatives were sought for urinary diversion of the exocrine secretions. By the late 1980s, surgical techniques were perfected: routine use of a whole organ and duodenal segment-to-bladder anastomosis.^{4,17–19} Those techniques led to increased acceptance of pancreas transplants. Further advances in imaging technology allowed for more accurate assessment and less invasive treatment of intra-abdominal complications (e.g., computed tomography [CT]-guided percutaneous catheter abscess drainage).²⁰ During the mid-1980s to early 1990s, better outcome also resulted from the introduction of cyclosporine, more potent, yet less toxic, antibiotics (e.g., cephalosporins), antifungal and antiviral agents, and advances in organ preservation and critical care of pancreas recipients.

However, those improvements in *early* postoperative morbidity and mortality associated with generalization of the bladder drainage technique came at the price of increased *late* morbidity. Up to 30% of all bladder-drained recipients experienced fluid and bicarbonate losses, hematuria, cystitis, and urethritis, eventually requiring conversion from bladder to enteric drainage.^{21–26} Conversion operations have low morbidity and nearly no mortality,^{21–26} but the complications lead-

FIGURE 9.2.2.1. Incidence of pancreas graft losses (SPK, PAK, and PTA) from surgical complications (technical failures) by era as reported by the UNOS US pancreas registry. Note that the overall technical failure rate for 1983 to 1987 cases was 25% (data not shown).^{1,11,233,234}

ing to conversion nonetheless led several transplant centers to reconsider enteric drainage in the early to mid-1990s.²⁶⁻³³ Thus, more than 30 years after the initial pancreas transplants were done with enteric drainage, the technical evolution has come full circle. Enteric drainage is currently used for over 50% of all pancreas transplants in the United States.¹¹ Still, it was with bladder drainage that transplant surgeons and physicians had the opportunity to perfect operative and immunologic outcomes and perioperative management.

Graft loss rates from surgical complications have drastically decreased, yet recent single-center reviews continue to report posttransplant relaparotomy rates as high as 25% to 50%. The significance of surgical complications persists even in the current era.^{29,30,34-41}

Pretransplant Surgical Complications

Pretransplant complications constitute a vastly unrecognized and underreported surgical complication category. Such complications occur most often during procurement of the pancreas graft. Pancreas recovery is one of the most complex solid-organ recovery procedures, irrespective of whether it is performed with the in situ or ex situ (after en bloc harvesting) dissection technique (see chapter 8.1.3).⁴² The most common injuries to the pancreas graft involve the pancreatic vasculature, followed by the duodenal allograft segment or the pancreatic capsule and parenchyma. Fortunately, the pretransplant bench preparation of the pancreas graft allows for recognition and correction of most such problems before implantation and reperfusion.

Inadvertent resection of a segment of the splenic artery can occur, sometimes as a result of an unrecognized posterior gastric artery.⁴³ If a splenic artery segment is missing, both cut ends can often be reanastomosed end to end primarily, after

careful stump mobilization.⁴³ Alternatively, a segment of donor external or internal iliac artery may be used to create an interposition graft (splenic artery-to-splenic artery). If a proximal splenic artery resection was inadvertently done, the Y-graft (in the case of a whole-organ graft) can be anastomosed directly to the distal of the two cut ends of the splenic artery.⁴⁴ If no suitable vascular grafts from the donor are available for reconstruction, the transplant may be able to proceed under certain circumstances, for example, after ligation of the cut ends of the injured splenic artery. If the pancreas tail remains viable after reperfusion, no further action is necessary; in that case, the inferior pancreaticoduodenal peripancreatic collateral network is sufficient to supply the pancreatic tail (via the dorsal pancreatic artery). If the pancreatic tail is not viable after reperfusion, a distal in situ pancreatectomy can be considered.

Other arterial vascular procurement complications can occur. For example, if the donor has a replaced right hepatic artery coming off as the first branch of the superior mesenteric artery (SMA), the SMA must be transected distal to the take-off of the right accessory hepatic artery (in the case of combined pancreas and procurement). In such a case, the inferior pancreaticoduodenal artery may be injured. In whole-organ pancreas grafts, the gastroduodenal artery is ligated when the pancreas and the liver are procured from the same donor, so the duodenum and pancreatic head may be partially or completely devascularized. The graft may then be salvaged by creating an interposition graft between the gastroduodenal artery stump and the side of the superior mesenteric or splenic artery using a donor external iliac artery conduit to revascularize the pancreatic head.⁴⁵

The key to diagnosing and handling vascular complications is manual pancreas graft perfusion on the back table. Preservation solution must be gently injected into the SMA and splenic artery stumps (see also chapter 8.1.3). The ease of the

perfusion (i.e., the pressure applied to the syringe) must be continuously assessed and the quantity of the portal venous effluent carefully observed. If no appropriate effluent flows out of the portal vein, the reason may be graft malperfusion or the lack of perfusion of either the pancreatic head or pancreatic tail; the cause may be a devascularizing injury. Under rare circumstances, a back-table methylene blue or renografin angiogram may help determine the extent of hypoperfusion and assess the vascular compromise.⁴⁶ After exact delineation of the underlying problem, either vascular reconstruction or nonuse of the pancreas graft must be considered.

A significant preoperative arterial vascular complication occurs when donor vessels are not included with the pancreas graft by the procurement team. If none of the donor iliac bifurcations is included with a whole-organ pancreas graft that requires arterial reconstruction, or if the donor vessels are not usable because of donor atherosclerosis, several options exist. A segment of the pancreas graft's distal SMA (if the mesenteric pedicle is left long enough at the time of procurement) may be used to create an interposition graft between the splenic artery and SMA.⁴⁷ Alternatively, a segment of splenic artery from the splenic hilum may be used between the pancreas tail and spleen.⁴⁸ Or, under exceptional circumstances, a segment of the recipient's inferior mesenteric vein may be used as an interposition conduit.

Preoperative venous complications are much rarer than arterial complications. The portal vein may be too short for anastomosis to the recipient venous outflow vessel. However, the decision to proceed with a venous extension graft is a serious matter because such grafts are associated with increased post-transplant portal vein thrombosis rates.⁷ Two alternative strategies may be employed either separately or in combination. One entails careful mobilization of the portal vein into the pancreatic parenchyma by ligating and dividing the first small side branches. In many cases, doing so mobilizes the portal vein sufficiently, allowing for easy anastomosis to the recipient venous outflow vessel. The second strategy entails complete mobilization of the recipient iliac vein (for pancreas grafts that are to be drained systemically), including ligating and dividing all internal iliac veins; doing so also facilitates safe portal-to-iliac vein anastomosis. For portally drained grafts, the portal vein length is usually less of an issue given the immediate proximity of the recipient superior mesenteric vein (or a large tributary) to the portal vein of the pancreas graft.

If the portal vein is too short and needs extension but no donor vein is available, a portal conduit may be constructed from a donor artery segment.⁴⁹

A pancreas that is to be discarded because of vascular injury may still be considered for an islet transplant. However, logistic issues and prolonged ischemia time will too often preclude this option.

Preoperative damage to the pancreatic capsule or pancreatic parenchyma is most common in the pancreatic tail region. Usually, such damage can be addressed by simple oversewing of the capsular injury. If the tail has been injured after removal of the spleen, it can be repaired with the fishmouth

technique, as described previously, using several interrupted 4-0 polypropylene sutures.⁵⁰

Intraoperative Complications

If the recipient native arterial vasculature is injured intraoperatively (e.g., due to a vascular clamp injury, or an arterial dissection of the common or external iliac artery), immediate repair is mandatory, either by percutaneous transluminal angioplasty and stenting, or, preferably, using autologous or heterologous conduits.^{51,51a} Often, the recipient internal iliac artery, which could be used as an interposition graft, is not an option because of severe atherosclerosis, so a segment of donor vasculature should be considered. If that is not an option, then a segment of polytetrafluoroethylene (PTFE) graft must be used. However, under those circumstances, special precautions must be taken to avoid any spillage of duodenal contents in the PTFE graft area during the transplant to prevent postoperative infectious and pseudoaneurysmatic vascular complications.

If complications pertaining to the recipient native iliac vasculature preclude pancreas graft revascularization through the iliac system, alternatives are available. Examples include anastomosis of the graft distal splenic artery to the recipient inferior mesenteric artery or the use of conduits providing inflow via the recipient's lower abdominal aorta.⁵²

A potentially lethal complication that can occur during the dissection of the recipient iliac vessels is hemorrhage due to loss of control over a divided internal iliac vein. Complete mobilization of the iliac vein is important to minimize post-transplant vascular graft thrombosis and requires division of most internal iliac vein branches. If the distal end of a divided internal iliac vein is not appropriately tied, suture-ligated, or clipped, potentially uncontrollable, life-threatening hemorrhage can ensue. The exact origin of the bleeding is difficult to identify once the vein stump has retracted into the perisacral tissues or sacrum. Surgical management of such bleeding may include application of suture ligatures, clips, absorbable gelatin sponges, or titanium thumbtacks. However, even with retrograde presacral dissection, finding the bleeding vein stump may be impossible. Under exceptional circumstances, it may be preferable to abandon the transplant and switch the focus to preserving the recipient's life; the bleeding area should be packed and a relaparotomy done within 48 to 72 hours after optimization of hemodynamic and coagulatory parameters.

Other intraoperative complications include immediate severe hemorrhagic reperfusion pancreatitis to the degree that immediate graft removal may be necessary. In less severe cases of hemorrhagic pancreatitis, peripancreatic drains may be inserted at the time of the transplant and a relaparotomy planned (see also chapter 8.2.2).

If the tail of whole-organ grafts fails to appropriately reperfuse intraoperatively, but the head of the pancreas and duodenum appear viable, then distal pancreatectomy may be an option. Similarly, if the head of the pancreas appears to be non- or malperfused, a Whipple procedure should be

considered as long as the splenic artery supply of the tail can be left intact.^{53,54} The resulting segmental pancreatic graft, consisting of the tail of the pancreas, can be drained either into the bladder (after adequate bladder mobilization) or into the jejunum. A duodenal segment of a whole-organ graft that appears to be nonviable or severely injured after reperfusion may require partial resection. If partial resection is not sufficient, subtotal resection of the duodenal tissue should be considered, leaving only a duodenal button around the major and minor papillae for enteric or bladder drainage.¹⁸ If subtotal duodenal resection is not an option, then, under exceptional circumstances, the pancreas graft might be salvaged by pancreatic duct injection with a polymer.^{3,16, 54a}

Type 1 diabetics, in particular those with nephropathy, have a high incidence of overt or occult coronary artery disease.^{55,56} Low-risk groups can be defined by preoperative cardiac testing (e.g., dipyridamole–thallium myocardial imaging) and coronary angiography.^{55,56} But, even patients who undergo pretransplant intervention to optimize their cardiac status (e.g., percutaneous angioplasty, coronary artery bypass grafting) remain at higher risk for adverse perioperative cardiac events. Severe intraoperative hypotension must therefore be avoided: It has in particular deleterious consequences for diabetic pancreas transplant recipients. One recent study found that most pancreas recipients experienced acute systemic vasodilation and hypotension after reperfusion of the pancreas graft.⁵⁷ Those pathophysiological changes, in the setting of suboptimal filling pressures and acute blood loss, can lead to major perioperative cardiovascular morbidity. They must be prevented by judicious intraoperative anesthetic and fluid management (guided, if indicated, by the readings from a pulmonary artery catheter).

Posttransplant Complications

Vascular Complications

Graft Thrombosis

As compared with other solid-organ grafts, pancreas grafts have the highest nonimmunologic graft failure rates, with vascular thrombosis as the leading cause. During the 1980s, many pancreas transplant centers in the United States and Europe reported graft thrombosis rates ranging between 10% and 35%.^{7,58–60} Despite notable improvements during the 1990s—in donor selection, operative technique, and perioperative thrombosis prophylaxis—early graft thrombosis remains, by far, the predominant cause of technical failure. According to a recent United Network for Organ Sharing (UNOS) US pancreas registry report, graft thrombosis accounted for over 70% of technical failures in each of the SPK, PAK, and PTA recipient categories.¹¹ For primary bladder- vs enteric-drained grafts, graft loss rates secondary to graft thrombosis were 5.0% vs 5.5% for SPK, 5.4% vs 8.9% for PAK, and 7.2% vs

11.6% for PTA recipients.¹¹ In contrast to other surgical complications after pancreas transplants, graft thrombosis is, with rare exceptions, irreversible and results in graft loss. It adds considerable morbidity and even mortality if it occurs early posttransplant and if the thrombosed pancreas graft is not removed promptly.^{7,8,10} For high-risk diabetic recipients in particular, preventing graft thrombosis, by recognizing and avoiding risk factors, helps improve graft survival rates and lower thrombosis-related morbidity. In the vast majority of cases, early graft thrombosis is not related to anastomotic or other technical problems but rather to the low-flow state of the pancreas, pancreatic edema and impaired microcirculation, local and systemic hypercoagulability, and a host of donor and recipient factors discussed below.⁷ Late graft thrombosis is most commonly associated with chronic and less frequently with acute rejection. Unfortunately, risk factor analysis is rendered difficult by the wide array of risk factors implicated in the pathogenesis of pancreas graft thrombosis.

Donor Risk Factors

Previous analyses demonstrated that donor selection is of utmost importance in minimizing the incidence of graft thrombosis.^{7,61} A cardiocerebrovascular cause of donor death and older donor age were identified as significant risk factors for graft thrombosis.⁷ Note that the thrombosis risk increases continuously with donor age but that there is no absolute age threshold above which the use of a particular donor should be ruled out. Rather, donor age must be considered in conjunction with all other adverse factors that may apply to a particular graft. Cadaver pancreas grafts that cannot be reconstructed using a segment of the donor iliac arterial system (secondary to atherosclerosis) were also shown to be at higher risk for graft thrombosis.⁷ Thus, grafts from older donors, in particular those with pre-existing atherosclerotic disease, should be viewed with great caution. Similarly, use of an aortic Carrel patch for the pancreas graft constitutes a significant thrombosis risk factor⁷; in general, a Carrel patch is only available when the donor's liver is not used. Diseases precluding the use of the donor liver (e.g., alcoholic cirrhosis, steatosis) usually also affect the pancreas (and its thrombosis propensity); therefore, the condition of the liver can serve as a surrogate indicator of pancreas graft quality. These considerations would obviously not apply if liver procurement is impossible because of a liver-specific condition (e.g., liver trauma).

Hemodynamic instability and massive volume resuscitation of the donor, causing pancreatic edema and impairing microcirculation, are also risk factors for graft thrombosis.⁷ Interestingly, a recent experimental study showed that donor treatment with vasopressin analogues also impaired microcirculation in donor pancreases.⁶² Future clinical studies on the consequences of pharmacological donor resuscitation will need to assess the effect on postreperfusion pancreatitis and graft thrombosis rates.

The donor pancreatectomy must be performed with minimal mechanical trauma to the pancreas to minimize direct vascular damage and the potential for postreperfusion pancreatitis—both of which are risk factors for graft thrombosis. For similar reasons, pancreatic perfusion pressure and flush volume should be limited.⁷ It is unclear whether the advent of the University of Wisconsin (UW) preservation solution has improved thrombosis rates. Its clinical introduction coincided with improved pancreatic transplant results for a variety of other reasons, so its true impact is difficult to assess. From a clinical perspective, however, all other preservation solutions are now of historical interest only. Still, UW solution has not eliminated the thrombosis problem, either experimentally or clinically.¹¹

Preservation time is also a significant risk factor for graft thrombosis.^{7,11,63,64} Interestingly, a recent UNOS registry report found no direct effect of preservation time on technical failure rates (including graft thrombosis) in PAK and PTA recipients.¹¹ In that report, prolonged preservation time was detrimental for SPK recipients but not for PAK and PTA recipients, a finding that may reflect a more conservative approach to accepting solitary pancreas donors where prolonged preservation is only used if all other factors are favorable.¹¹ Discussion of the effects of preservation also needs to take into account center effects. A previous analysis of UNOS pancreas registry data showed a significant center effect regarding the importance of preservation time on pancreas graft outcome.⁶⁵ Larger centers (those with 50 or more pancreas transplants per year) saw no detrimental effect of increased preservation time on graft outcome, but smaller centers (those with 49 or fewer pancreas transplants per year) did.⁶⁵ Overall, it appears prudent to minimize preservation time, just as with any other organ transplant. Both preservation injury itself and graft pancreatitis may result from prolonged preservation time, and both are significant risk factors for graft thrombosis.^{7,11,63–66}

Recipient Risk Factors

Diabetic solid-organ recipients represent a challenging population with respect to their pre-existing hypercoagulability and their tendency to have higher platelet counts, in particular in the setting of end-stage renal disease (ESRD).^{67,68} Moreover, in one study a hypercoagulable state was observed via thromboelastography in insulin-dependent diabetic patients with ESRD undergoing SPK transplants.⁶⁹

Throughout the 1990s, the impact of recipient category on graft thrombosis rates considerably diminished.^{11,60,70} The historically invoked beneficial impact of uremia on thrombotic solid-organ graft complications does not seem to be a significant factor in pancreas recipients anymore.⁷ Currently, at least for primary bladder-drained grafts, thrombosis rates are similar for SPK (5.0%) and PAK (5.4%) and slightly higher for PTA (7.2%), recipients.¹¹ In contrast, the difference remains marked for primary enteric-drained grafts: SPK (5.5%), PAK (8.9%), and PTA (11.6%).^{11,33} The higher thrombosis rates reported with enteric drainage in solitary

pancreas recipients, however, may not be due to classic surgical, technical, or donor risk factors.³³ Rather, diagnosing a rejection episode is more difficult in solitary pancreas recipients because neither urinary amylase nor serum creatinine (i.e., of a simultaneously transplanted kidney from the same donor) can be monitored for rejection. A recent histopathologic analysis of explanted pancreases that had failed early posttransplant suggested that, in one third of them, the cause for graft thrombosis was, in fact, rejection.⁷¹ Thus, the classic distinction between nonimmunologic and immunologic graft failure is moot. Future analyses of pancreas graft outcomes must take this confounding factor into account.

For uremic recipients on dialysis at the time of their transplant, the kidney transplant literature suggests that peritoneal dialysis is associated with higher graft thrombosis rates.⁷² Peritoneal dialysis patients have significantly higher concentrations of thrombogenic apolipoprotein(a). They also have higher procoagulant activities of Factors II, VII, VIII, IX, X, XI, and XII, whereas endogenous anticoagulants, such as protein C and antithrombin III, are not altered.⁷² Peritoneal dialysis is also associated with higher hematocrit levels due to reduction of extracellular volume, so patients may be at greater risk for being hemoconcentrated.⁷² Finally, peritoneal dialysis may be a surrogate marker for loss of hemodialysis access options due to repetitive thrombosis of dialysis access grafts and fistulas secondary to a hypercoagulable state. However, in the pancreas transplant literature an adverse effect of peritoneal dialysis on graft thrombosis has, thus far, not been reported. Nevertheless, when considering a particular donor organ for a particular recipient, including the recipient's dialysis mode in the overall risk assessment for graft thrombosis appears prudent.

Preoperative recipient evaluation must also screen for the presence of a hypercoagulable state, such as the antiphospholipid syndrome. If a hypercoagulable state cannot be ruled out, peri- and long-term postoperative management should include recipient anticoagulation.^{72a}

In one large, single-center, multivariate analysis, a retransplant was noted to be a risk factor for graft thrombosis in SPK but not in PAK and PTA recipients.⁷ This finding, which was not observed at other centers, may not be intrinsic to the SPK recipient category but rather may reflect the more liberal donor acceptance criteria for SPK organs at that particular center. The discrepancy re-emphasizes the importance of considering all potential risk factors and covariates when making a global thrombosis risk assessment for a given donor–recipient combination.

A number of investigators have noted higher thrombosis rates for segmental (vs whole-organ) grafts.^{2,66,73,74} Segmental grafts may be more prone to thrombosis because the short splenic artery and vein stumps of segmental grafts allow for less spatial flexibility and may be more prone to bending and twisting. In addition, *in situ* the native pancreatic body and tail are also supplied through the transverse or dorsal pancreatic artery, which receives collateral flow from the SMA.^{74a} This artery is usually not primarily revascularized in segmental grafts. The blood supply of a segmental pancreatic

body and tail is, therefore, critically dependent on a single vessel, relying on flow only through side branches of the splenic artery. As a result, any partial or complete thrombosis of the splenic artery or its small side branches would be more detrimental in segmental grafts.⁷ In contrast, in whole-organ grafts collateral flow through the transverse pancreatic artery may continue to perfuse the pancreatic tail even if the splenic artery has thrombosed. Finally, a segmental pancreas graft is an even lower-flow system than a whole-organ pancreas graft, rendering it more susceptible to thrombotic complications. Hence, it is not surprising that even in current segmental pancreas transplant series thrombosis rates as high as 19% are still reported.⁷³

As compared with other solid-organ transplants, pancreas transplants are also unique with regard to the frequent need for arterial reconstruction. Combined liver and en bloc pancreas procurement has now become the rule, so an *ex situ* reconstruction of the dual blood supply of the pancreas becomes necessary when whole-organ grafts are used and when the celiac axis is retained with the liver (as is routine).⁴² A large multivariate analysis demonstrated that Y-graft reconstruction has the lowest thrombosis risk. That finding may seem paradoxical because the Y-graft involves creation of two (potentially thrombogenic) anastomoses vs only one anastomosis with an end-to-side graft or vs no additional anastomosis when an aortic Carrel patch is available.⁷ However, the availability of a Y-graft usually indicates the absence of significant donor atherosclerotic disease (a risk factor for graft thrombosis). More important, an end-to-side anastomosis or an interposition graft allows for less spatial flexibility than a Y-graft when an anastomotic site in the recipient is chosen. An end-to-side anastomosis or interposition graft may therefore predispose the arterial vascular pancreas inflow system to bending or twisting and increase the risk for thrombosis.⁷

Available portal vein length is usually not an issue, even with combined liver and en bloc pancreas procurement. Ideally, the portal vein should be left as short as possible in the recipient anyway to avoid kinking, bending, or twisting. However, with unusual graft placement (e.g., on the left side, where the iliac vein takes a more posterior, deeper course) a portal vein extension graft may become necessary. One large study suggested that the use of portal vein extension grafts is associated with higher graft thrombosis rates. It is unclear whether the increased rates are due to the additional (potentially thrombogenic) anastomosis in the low-flow portal venous outflow tract, mechanical kinking of the portal vein extension conduit, or suboptimal mobility of the donor venous outflow vessel (e.g., left iliac vein) and suboptimal spatial anastomotic configuration.

Of note, thrombosis rates are not significantly different for grafts with the venous effluent drained portally vs systemically.¹¹

According to a large multivariate single-center analysis of over 400 pancreas transplants done during the cyclosporine

era, the implantation site of choice for systemically drained pancreas grafts in the recipient is the right iliac system, after complete mobilization of the right iliac vein.⁷ This site allows for creation of a tension-free portal venous anastomosis, lateral to the common or proximal external iliac artery on the right side, at the same level in a sagittal direction as the arterial anastomosis. However, if a kidney graft was previously placed on the right side, or with a retransplant (where the right-sided iliac vasculature cannot be used because it is too hazardous to remove the previous pancreas graft), then the left iliac system or aorta must be used. The left iliac arterial system can be fraught with notable difficulties when used for inflow. First, the sigmoid colon is on the left side and the pancreas has to be positioned medially (e.g., onto the common iliac artery) or laterally (e.g., onto the external iliac artery). Left medial placement increases the distance between the donor duodenum and recipient bladder for bladder-drained grafts, creating the potential for tension and traction on both bladder and vascular anastomoses.⁷

More important, the left common iliac vein takes a much more posterior (in a sagittal direction) course than its right counterpart. In addition, the left iliac vein is tethered by the left internal iliac artery. It may be disadvantageous to divide the left internal iliac artery in diabetics who may have occlusion of the contralateral internal iliac artery; instead, it may be necessary to rely on the collateral inflow through the left internal iliac artery for part of the blood supply to the lower body. The portal vein anastomosis to the common iliac vein on the left side is invariably more posterior and deeper than the arterial anastomosis (unless patency of the right internal iliac artery is assured and the left internal iliac artery can be ligated and divided). Thus, portal venous extension grafts must be used more frequently—an independent thrombosis risk factor. Another problem when placing the pancreas graft on the left side is that the left common iliac artery may impinge on the portal vein as it courses in an anteroposterior direction toward the (deeper) left common iliac vein.⁷

Placing the pancreas graft lateral to the sigmoid colon onto the left external iliac vasculature is potentially even more disadvantageous because positioning the graft in this relatively restricted space may be difficult. Further, the left external iliac vein does not run parallel to the left external iliac artery. Instead, it follows a more posterior–anterior course as it exits from under the left internal iliac artery deep in the pelvis and then toward the more superficial left inguinal ligament, in particular in male recipients. This course, again, renders the portal venous anastomosis more difficult and the portal vein more susceptible to impingement by the left external iliac artery. It is therefore not surprising that left-sided pancreas graft placement is a significant risk factor for thrombosis.⁷ Alternative solutions may include using the aorta as an inflow vessel if a right-sided iliac pancreas implantation is not possible or, in selected cases, using the inferior mesenteric artery.⁵² Under those circumstances, drainage of the graft portal vein into the recipient's portal circulation and enteric

TABLE 9.2.2.1. Perioperative pancreas graft thrombosis prevention (modified University of Minnesota protocol).

Intraoperatively

If left-sided iliac pancreas graft placement: ligation and division of left internal iliac artery and full mobilization of left iliac vein (unless right internal iliac artery was previously ligated)

If recipients are not on dialysis at the time of their transplant: systemic heparinization before aortic or iliac cross-clamping (heparin 50–70 U/kg IV bolus)

Postoperatively

Systemic heparinization

If no evidence of postoperative bleeding: heparin 1–3 U/kg/h IV continuous infusion, beginning immediately postoperatively

Gradual increase of heparin up to 7–10 U/kg/h IV continuous infusion, beginning postoperative d 2–3

Discontinuation of heparin infusion on postoperative d 7

Acetylsalicylic acid 325 mg every day indefinitely (PR postoperative d 1–3; PO thereafter)

If a retransplant or if a history of prior graft thrombosis or of other significant thrombotic event: warfarin PO beginning postoperative d 3, with dose adjusted to achieve a target INR of 2.0–3.0 (depending on the indication, until 6 mo postoperatively or indefinitely)

Source: Adapted from Troppmann et al.⁷ and Kandaswamy et al.⁷⁰ PR, per rectum; PO, per os; INR, international normalized ratio of prothrombintime.

drainage of the exocrine secretions is an option that should be considered, especially for SPK recipients.

A recent analysis during the tacrolimus era suggests that left-sided pancreas graft placement may result in acceptable thrombosis rates provided that the left internal iliac artery is divided, the left iliac vein is completely mobilized, and perioperative anticoagulation is used (Table 9.2.2.1).⁷⁵ In any event, with the more frequent application of PAK transplants for type 1 insulin-dependent diabetes left-sided kidney graft placement should be routine if a later pancreas transplant is contemplated.⁷

Posttransplant graft pancreatitis is also associated with graft thrombosis and may be related to donor risk factors (e.g., hemodynamic instability, vasopressor administration), procurement injury (excessive intraoperative mechanical manipulation), perfusion injury in the donor (e.g., excessive amounts of flush volume, high perfusion pressure), preservation injury, or ischemia-reperfusion injury (reflecting total cold and warm ischemia time).^{7,62–64,66,76} In experimental acute pancreatitis models, vasoconstriction, intravascular coagulation, and increased endothelial permeability may result in increased pancreatic edema and impaired venous drainage. Ensuing pancreatic ischemia may then trigger the transition from mild to severe pancreatitis. With increasing severity of pancreatitis, pancreatic microcirculation is progressively impaired and necrosis and graft thrombosis may occur.

Analysis of the effects of graft pancreatitis and graft thrombosis is impeded by the lack of a consistent, accurate definition of graft pancreatitis. Serum amylase levels (which are frequently used to assess for graft pancreatitis, both clinically and experimentally) may not reflect the degree of pancreatitis and its impact on microcirculation appropriately. Never-

theless, several studies suggest that graft pancreatitis is associated with increased graft thrombosis rates.^{7,63,64,66} Therefore, all efforts must be made to avoid graft pancreatitis to begin with.

The impact of recipient immunosuppression on pancreas graft thrombosis rates remains unclear. Some kidney transplant studies suggest that kidney graft thrombosis rates are adversely affected by the administration of cyclosporine.⁷⁷ Experimental evidence suggests that cyclosporine decreases prostacyclin synthesis. In addition, cyclosporine may cause direct endothelial damage, increase thromboxane A₂ production, and adversely alter fibrinogen, circulating monocyte procoagulant activity, protein C, factor VIII-related antigen, factor VIII coagulant-activity, and adenosine diphosphate (ADP)-induced platelet aggregability.^{7,78–81} Experimentally, the combination of preservation injury and subsequent administration of cyclosporine increases thromboxane A₂ production.⁸² Finally, chronic exposure to cyclosporine and steroids may exhaust prostacyclin formation pathways.^{7,78}

It is unclear to what extent the above drug-related mechanisms affect thrombosis rates in *pancreas* recipients. A recent multicenter study suggests higher pancreas graft thrombosis rates in recipients who were treated with cyclosporine (vs tacrolimus).⁸³ Interestingly, two case series of splenic vein thrombosis in recipients on intravenous (IV) tacrolimus have also been reported.^{84,85} Similar to cyclosporine, tacrolimus may induce vasospasm (resulting in microvascular injury) and may cause direct endothelial injury and thrombosis (secondary to alterations in the thromboxane A₂–prostacyclin [PGI₂] balance or to endothelin release).⁸² Of note, in one case series the graft thromboses observed under IV tacrolimus treatment occurred during simultaneous treatment with interleukin-2 receptor antibodies.⁸⁴

Any impact of newer immunosuppressants, such as sirolimus, on graft thrombosis rates has yet to be established. Of concern, a recent multicenter liver transplant study noted an increased incidence of hepatic artery thrombosis in sirolimus recipients.⁸⁶ Clearly, further study is required with a large number of patients and multicenter data to determine the optimal immunosuppressive regimen for minimizing graft thrombosis rates.

Clinical Diagnosis

About 60% of all thromboses are venous and 40% are arterial; but, exact distinction is at times difficult, even when examining the explanted pancreas. The vast majority of thromboses (>70%) occur within the first week posttransplant. Clinical symptoms of graft thrombosis include graft tenderness, unexplained hyperglycemia, rapidly and unexpectedly increasing insulin requirements, unexplained hemoperitoneum (after venous graft thrombosis), thrombocytopenia, leukocytosis, dark hematuria (with venous thrombosis of bladder-drained grafts), and rapidly declining or absent urinary amylase levels (for bladder-drained grafts only). In some

recipients, a secondary deep venous thrombosis of the ipsilateral ileofemoral venous system may develop (by retrograde portal vein thrombus propagation); this may even be the initial symptom. Diagnosing acute vascular graft thrombosis may at times be difficult because the clinical symptoms are nonspecific. It is therefore in particular important to include a thrombotic event in the array of differential diagnoses when encountering any of the previously mentioned symptoms during the early posttransplant period. Clinically suspected graft thrombosis is usually confirmed readily by color duplex Doppler ultrasonography, which can visualize the graft in- and outflow vessels and the vascular anastomosis.^{87,88} Absence of flow in the arterial inflow vessel or venous outflow vessel, or both, strongly suggests primary vascular thrombosis. Importantly, severe pancreatitis or rejection may also present with a markedly diminished and at times difficult to detect flow.

The diagnostic accuracy and sensitivity of the two most frequently obtained pancreas graft imaging studies—color duplex Doppler ultrasonography and radionuclide perfusion scintigraphy—can be substantially increased if done serially.^{7,88} Contrast-enhanced CT, which can selectively visualize the graft during contrast bolus administration, may be helpful in selected patients, but its usefulness is limited by the nephrotoxic side effects of IV contrast agents. Those side effects are in particular undesirable for pancreas recipients with kidney grafts (SPK, PAK) or with native kidneys that suffer from varying degrees of diabetic nephropathy (PTA). Computed tomography is in general more useful in diagnosing other postoperative complications (such as fluid collections, pancreatitis, or abscesses) than in diagnosing graft thrombosis.^{7,88} The role of magnetic resonance angiography (MRA) in diagnosing pancreatic vascular complications expanded in the 1990s^{89,90}; MRA is advantageous because it does not use nephrotoxic contrast agents. The gold standard, albeit relatively rarely used for confirming graft thrombosis, is conventional angiography.^{7,88} Surgical exploration remains the ultimate diagnostic modality; it allows simultaneous diagnosis and initiation of treatment.

Treatment and Prevention

Therapeutic options for thrombosed pancreas grafts are limited. If the thrombosis occurs early posttransplant and involves only the venous system in whole-organ grafts, venous thrombectomy can be attempted, in particular if the pancreatic tail is still viable.^{91–94} However, only anecdotal case reports have been published of salvage after thrombectomy of pancreas grafts with partial or complete venous thrombosis.^{91–95} Key prerequisites for salvage are immediate relaparotomy on diagnosis of the thrombotic event and a noncompromised pancreatic parenchyma. If partial portal or isolated complete splenic vein thrombosis in a whole-organ graft is documented by duplex Doppler ultrasonography, systemic anticoagulation (with or without thrombolytic therapy of the recipient) may

maintain the viability of the pancreas graft without operative reintervention, especially if long-term anticoagulation is instituted.^{93–96}

There are no known cases of pancreas graft salvage after complete arterial graft thrombosis. At least two cases of salvage were reported after partial arterial graft thrombosis, with thrombectomy of the splenic artery and SMA, respectively, in whole-organ grafts without postoperative complications.^{97,98} If only the splenic artery of a whole-organ graft is thrombosed, the graft may be converted to a segmental graft by performing an *in situ* distal pancreatectomy. However, the morbidity and mortality rates are potentially high due to severe ischemic graft pancreatitis after a salvage procedure for partial or complete venous or arterial pancreas graft thrombosis: At least two cases of postoperative acute respiratory distress syndrome and one death have been reported.⁹¹

By far the most common treatment after acute graft thrombosis is graft pancreatectomy.^{7,9,99–102} Early posttransplant, once graft thrombosis is diagnosed, relaparotomy, and, if necessary, graft pancreatectomy, should be done promptly. Otherwise, infectious complications can have a significant impact on morbidity and mortality.^{7,8,10} In fact, graft thrombosis is still the most common indication for graft pancreatectomy.^{9,99–102} In recipients with late graft thrombosis from chronic rejection or progressive graft arteriopathy, graft pancreatectomy may not always be necessary, especially if the vascular occlusion process is sufficiently slow to allow for graft atrophy and fibrosis.

Some authors have proposed proceeding with graft pancreatectomy and an immediate retransplant if graft thrombosis occurs within the first 4 weeks posttransplant.^{93,94,103–105} Despite several optimistic case reports,^{93,94,103–105} concerns remain regarding increased morbidity and mortality. With whole-organ grafts including the donor duodenum, in particular those with enteric drainage, contamination and colonization of the peritoneal cavity after the first graft may have deleterious consequences with respect to infectious complications after the second graft.⁸ Many surgeons advocate performing the retransplant at a later time, after the recipient completely recovers from the thrombotic event.

Numerous attempts have been made at prophylaxis and prevention of graft thrombosis.⁷ Most important, routine perioperative anticoagulation has been advocated, using IV heparin at subtherapeutic doses or low-molecular-weight dextran and short- and long-term acetylsalicylic acid with or without long-term full anticoagulation with warfarin. Based on pathophysiological considerations, it is apparent that posttransplant prophylaxis for thrombosis should include platelet aggregation inhibitors to counteract the consequences of abnormal eicosanoid synthesis by recipient-derived circulating cells and donor-derived vascular graft endothelium.⁷ The University of Minnesota group feels that their empirical perioperative low-dose heparin and acetylsalicylic acid protocol significantly contributed to a marked decrease of thrombotic complications in the 1990s (Table 9.2.2.1).⁷⁰ Many centers

use perioperative antithrombotic prophylaxis to varying degrees, but any anticoagulation protocol for pancreas recipients has yet to be proven safe and effective in a prospective randomized study. For now, low-intensity perioperative anticoagulation seems wise (Table 9.2.2.1). Without a doubt, an increased relaparotomy rate for bleeding—an unavoidable consequence of any perioperative anticoagulation—is more tolerable than an unacceptably high graft pancreatectomy rate due to graft thrombosis.

Disappointingly, no substantial clinical proof exists of the efficacy of graft thrombosis prophylaxis by preventing or treating posttransplant pancreatitis, for example, with the long-acting somatostatin analog octreotide.^{106–108} Another approach aimed at mitigating the effects of preservation and reperfusion injury is calcium channel blocker administration, which has been successfully used clinically in kidney recipients. In a retrospective study the incidence of graft pancreatitis significantly decreased when calcium channel blockers were administered in the immediate postoperative period.⁶³ But, their effects on the incidence of graft thrombosis were not explicitly described and so remain unclear.⁶³ All of the above findings and the assessment of other novel anticoagulants and platelet aggregation inhibitors await further investigation, especially in large-animal and clinical studies.

Currently, the best available strategy to prevent graft thrombosis begins with judicious donor selection, carefully reconsidering the use of older donors and of those who died of cardiocerebrovascular causes. Procurement techniques must be atraumatic. Perfusion pressure, flush volume, and preservation time must be minimized. Arterial reconstruction of whole-organ pancreas grafts should preferentially be done using a Y-graft. Extension grafts of the portal vein must be avoided if at all possible. In the recipients, pancreas grafts should not be anastomosed to the left common internal or external iliac artery; if this is not possible (e.g., because of a previous right-sided kidney transplant), the distal abdominal aorta is a safe alternative. If left-sided pancreas graft placement is unavoidable, division of the left internal iliac artery must be strongly considered to increase mobility of the left iliac vein. All efforts must be directed at decreasing the incidence and severity of graft pancreatitis. Empirical data suggest that perioperative low-intensity anticoagulation, in conjunction with antiplatelet therapy, can help decrease graft thrombosis rates further. Selected recipients may require full anticoagulation.^{72a}

Late Vascular Complications

Atherosclerotic disease of the recipient or donor vasculature leading to preanastomotic, anastomotic, or postanastomotic stenosis, respectively may present with endocrine graft dysfunction and, on occasion, hyperamylasemia.^{74a,109} With bladder-drained grafts, symptoms may include exocrine dysfunction with decreasing urinary amylase production. Posttransplant progression of pre-existing intra-graft donor vascular disease can result in similar findings. The chronic occlusive arterial vascu-

lopathy seen with “chronic” pancreas graft rejection is at times indistinguishable from pre-existing vascular disease processes. Interestingly, the arterial tree of duct-injected grafts may be more prone to develop late occlusive arterial disease, presumably secondary to the fibrosis of the surrounding exocrine tissue.¹¹⁰

All these complications can eventually result in graft thrombosis and may require graft pancreatectomy. If there is a well-defined lesion in the proximal portion of the pancreas graft arteries, then percutaneous transluminal angioplasty may be attempted, with or without endovascular stenting.¹¹⁰ For recipients with chronic diffuse arteriopathy and progressive graft dysfunction, the only options are return to insulin therapy and a retransplant.¹¹¹

Any recipient with new onset of a bruit over the pancreas graft should undergo color duplex Doppler ultrasonography to rule out a pseudoaneurysm or an arteriovenous fistula (AVF).¹¹² Pseudoaneurysms can present as an arteriovesical or arterioenteric fistula and can occur many years posttransplant, even in pancreas grafts that no longer function because of chronic rejection.¹¹³ Importantly, pseudoaneurysms can also occur years after transplant pancreatectomy.¹¹⁴

Pseudoaneurysms are highly morbid, potentially life-threatening complications and have typically a bacterial or fungal infectious etiology. Interestingly, at least one case of an arterioenteric fistula that was possibly caused by a cytomegalovirus (CMV) infection of the donor duodenum was reported.¹¹⁵ However, there are also isolated case reports of sterile pseudoaneurysms caused by a surgical or technical anastomotic problem or by an infection that cleared with antibiotic treatment, resulting in a “sterile” pseudoaneurysm.^{116,117} Pseudoaneurysms can arise from the graft splenic artery or SMA, vascular reconstruction (e.g., Y-graft or interposition graft), iliac artery anastomosis, or recipient native iliac artery (distant from the anastomosis).^{113–121} In cases occurring late after transplant pancreatectomy, the pseudoaneurysm originates at the anastomotic site where the aortic Carrel patch or an arterial segment of the donor pancreas vasculature was left in place (when proceeding with arterial ligation and vascular division during the transplant pancreatectomy). It has been suggested that pseudoaneurysms occur more frequently with enteric-drained grafts.¹¹⁴ Initially, they may be asymptomatic or may present unspecifically with endocrine or exocrine insufficiency. Eventually, they result in pain over the pancreas graft, gross hematuria (if they penetrate the bladder), acute lower-gastrointestinal bleeding (if they erode into the intestine), a palpable pulsatile mass, sepsis, and, at the time of rupture, hemodynamic instability.^{113–121} Symptomatic pseudoaneurysms usually indicate impending or acute rupture. Some are discovered incidentally by color duplex Doppler ultrasonography, which is also the diagnostic screening modality of choice.¹¹⁸ Contrast-enhanced CT, MRA, and conventional angiography are used for confirmation and exact anatomic definition as indicated. If the recipient is stable and the pseudoaneurysm asymptomatic, conventional angiography is indicated to determine the location and extent of the pseudoa-

neurysm and rule out an AVF secondary to the pseudoaneurysm.¹¹⁸ If there is no clinical evidence of an acute infectious cause (i.e., in the case of “sterile” pseudoaneurysm), endovascular stenting has been successfully attempted in at least one case.¹¹⁶

In all other cases, prompt operative re-exploration is mandatory.¹¹⁸ Usually, with impending or ongoing acute pseudoaneurysm rupture, graft pancreatectomy is necessary. Intraoperatively, preliminary proximal and distal arterial and venous control of the recipient vasculature is key. In the face of acute infection, construction of extra-anatomic bypasses (either axillofemoral or femorofemoral) is often necessary because implantation of PTFE grafts to replace the ligated or resected recipient vasculature is contraindicated. In rare cases of ruptured pseudoaneurysms that do not involve infection, the graft can be salvaged operatively. The graft must be thoroughly mobilized to gain access to the diseased vascular segments. A temporary takedown of the duodenovesical or duodenojejunal anastomosis may be necessary to allow unimpeded, full inspection of, and access to, the back side of the pancreas graft and peripancreatic vasculature. Fortunately, the incidence of this complication appears to have diminished over time, possibly due to an overall lower infection incidence in current case series: Most cases of pseudoaneurysm are reported in the earlier pancreas transplant literature throughout the 1980s into the early 1990s.^{113–121}

An AVF is another rare vascular cause of pancreas graft dysfunction.^{112,122–125} It can occur as early as a few hours posttransplant to as late as many years posttransplant.^{112,122–124} Typically, the fistula occurs in the ligated or stapled distal mesenteric vascular bundle in whole-organ grafts.^{112,122–124} It is unclear from the available literature whether this complication occurs more frequently with mass stapling or with blind mass ligation (using several individual tie ligatures or suture ligatures) of the mesenteric vascular bundle. AVFs may also be related to transcystoscopic–transduodenal or percutaneous pancreas biopsies.

An AVF may cause endocrine dysfunction, new onset of a bruit over the graft, hematuria, or a palpable thrill.¹²² It may be incidentally discovered during color duplex Doppler ultrasonography. In selected cases, an AVF in the mesenteric bundle may cause vascular steal, with sonographically nondemonstrable flow in the splenic vein of the pancreas graft.¹²³ Angiography is used to confirm the diagnosis.

The first-line treatment is percutaneous transarterial embolization of the AVF, which has been successful in several cases.^{112,123–125} If this approach is technically not feasible or fails, re-exploration of the pancreas graft is necessary with direct surgical suture ligation of the AVF using, if necessary, intraoperative color duplex Doppler ultrasonography.¹²²

True intrapancreatic arterial aneurysms are rare. It is unclear if they represent a pre-existing donor aneurysm or arise de novo in the recipient. Typically, they are observed in the splenic artery.¹²⁶ Once they are diagnosed, embolization should be attempted. Surgical resection is indicated for

aneurysms that are not amenable to percutaneous treatment. For proximal splenic artery aneurysms, embolization, ligation, or resection may lead to ischemia of the pancreatic tail and may require partial pancreatectomy.

Vascular Kidney Graft Complications in Pancreas Recipients

A unique vascular complication after solid-organ transplants is the torsion of the renal vascular pedicle in SPK recipients. This rare complication is due to the excessive mobility of intraperitoneally placed kidney grafts (in particular of left kidneys with their longer vascular pedicle) at the time of the pancreas transplant.^{127,128} As opposed to extraperitoneal kidney grafts, intraperitoneal kidneys may rotate and torse around their vascular pedicle axis, in particular if the transplant ureter is long, the recipient’s bladder is floppy, and no adhesions have formed (e.g., secondary to steroid treatment).^{127,128}

The onset of symptoms occurs typically between several months posttransplant and as late as 2 years posttransplant.^{127,128} Symptoms can indicate graft dysfunction, hydronephrosis, or partial or complete renal vein thrombosis, with sudden onset of hematuria, pain over the kidney graft, or sudden cessation of urine output.^{127,128} If renal pedicle torsion is suspected clinically and confirmed by color duplex Doppler ultrasonography, immediate relaparotomy may salvage the kidney graft. Renal pedicle torsion may be prevented for intraperitoneally transplanted kidneys, in particular those with a long vascular pedicle, by performing a nephropexy to the recipient’s retroperitoneum or anterior abdominal wall and keeping the transplant ureter as short as possible.^{127,128} Alternatively, the kidney graft can be placed extraperitoneally after dissecting an extraperitoneal pocket over the external iliac vessels through the same midline incision that is also used for intraperitoneal pancreas placement contralaterally.¹²⁹

Other vascular complications pertaining to kidney grafts (e.g., renal artery stenosis, AVF) are not specific to pancreas recipients and should thus be handled as in any solitary kidney recipient.

Surgical Wound Infections

Surgical wound infections can be divided into two categories: superficial and deep-wound infections. Superficial infections are addressed elsewhere (chapter 9.2.3). Most wound infections after pancreas transplants are deep (intra-abdominal) wound infections, either alone or combined with superficial infections. In one large series, 70% of all wound infections were deep (45%, deep only; 25%, combined deep and superficial) and 30% were superficial.¹³⁰

Intra-abdominal infections, together with graft thrombosis, comprise one of the most significant complications after pancreas transplants.^{5–8,10,11} Graft thrombosis leads to high rates of graft loss, but no added mortality if handled appropriately.^{7,10} Intra-abdominal infections lead not only to high rates

of graft loss, but also to substantial mortality.^{5,6,8,10,130,131} Fortunately, over the past decade the most significant and dramatic progress—with regard to reducing posttransplant surgical complications and technical failures—has been made with intra-abdominal infections.^{1,6,8,10,11,132–134}

In a historic study from the University of Minnesota, the incidence of intra-abdominal infections was 22% and the mortality rate for recipients with such infections was 27%, up to the mid-1980s.⁵ A decade later, during the cyclosporine era, those findings were still nearly unchanged in another review by the same group: The incidence of intra-abdominal infections was 20%.²⁰ In that same cyclosporine-era study, intra-abdominal infections were associated with dismal patient and graft survival rates.¹⁰ Overall patient survival at 1 and 3 years posttransplant was 76% and 74% for recipients with infections vs 92% and 84%, respectively, for those without. Even more disconcerting, for recipients with fungal intra-abdominal infections graft survival at 1 year was 17% (vs 63% for those without infection); the mortality rate was 20% for recipients with sole fungal or combined fungal and bacterial infections.^{6,10} Relaparotomy was required in 90% of the recipients with intra-abdominal infections; of those undergoing relaparotomy, graft pancreatectomy was performed in 70%.¹⁰

More recently, several studies have reported substantially improved rates of intra-abdominal infections, morbidity, and mortality.^{132–134} United Network for Organ Sharing pancreas transplant registry data also point to improvement.^{1,11} In the 2001 UNOS registry analysis, the graft loss rate from infection and pancreatitis ranged from 0.6% to 2.0%, depending on recipient category and exocrine secretion drainage method.¹¹ These dramatic improvements are the consequence of standardized surgical techniques, optimized perioperative antimicrobial and fungal prophylaxis, more specific immunosuppression (resulting in lower rejection rates and less requirement for mono- or polyclonal anti-T-cell therapy), and, probably most important, better donor selection. For recipients who still develop intra-abdominal infections, improved imaging techniques allow earlier diagnosis, more accurate delineation of the pathology, and even better treatment (e.g., percutaneous abscess catheter drainage),²⁰ all of which have considerably contributed to better outcomes. The combination of these measures has reduced the rate of intra-abdominal infections to less than 15% and the rate of graft loss to a remarkably low level (as cited above).^{11,132–134}

Risk Factors for Intra-Abdominal Infection

From a review of the currently available evidence, several risk factors for intra-abdominal infections emerge. Arguably, donor risk factors are most important. Older donors (in particular those older than 45), obese donors with an elevated body mass index, and longer preservation times have all been associated with increased rates of intra-abdominal infections.^{10,64,130,135,136} Recipient risk factors associated with in-

creased rates include a retransplant, pretransplant peritoneal dialysis, older age, use of the duodenal button (vs the duodenal segment technique), a segmental pancreas transplant (in particular with a living donor), longer operating time, and retroperitoneal pancreas placement.^{10,11,83,99,130,137–145} Graft loss from intra-abdominal infections is in itself a significant risk factor for intra-abdominal infections in retransplant recipients.¹⁴⁶ Of note, in most retransplant recipients intra-infections posttransplant are caused by the same microbial species that caused failure of their previous graft, even after an interval of 1 to 5 years.¹⁴⁶

Another important posttransplant risk factor for intra-abdominal infections is an anastomotic or duodenal segment leak: About 30% of all intra-abdominal infections are associated with a leak.^{10,147} Yet another important risk factor is posttransplant pancreatitis, which is difficult to quantify clinically.¹³⁵ Postreperfusion pancreatitis activates and liberates pancreatic enzymes that provoke inflammation and necrosis in the tissues surrounding the pancreas graft (peripancreatitis). The result is an excellent growth medium for microbes, which can lead to either diffuse or localized intra-abdominal infections.¹³⁰ Because infections are so commonly associated with pancreatitis and peripancreatitis, and because infections themselves can cause peripancreatitis, distinguishing the inciting event is at times difficult in a particular recipient. Therefore, these two complications are often grouped into a single technical failure category, such as in the UNOS pancreas registry reports.¹¹

In the current era, the exocrine secretion drainage method does not appear to affect the rates of intra-abdominal infections or technical failure. Historically, higher rates of intra-abdominal infections were observed with enteric-drained grafts, but this difference has not persisted in more recent case series.^{2–5,13,28–35,148} Drainage of the exocrine secretions into the stomach, a technique now of historic interest only, was associated with high bacterial peritonitis rates, in particular in recipients with graft pancreatitis: Presumably, the inflamed pancreas in direct contact with the transverse colon led to local translocation of luminal colonic microbes.² Positive duodenal cultures obtained from duodenal donor segments are not predictive of intra-abdominal infections.¹⁴⁹ However, for recipients who develop intra-abdominal infections the microbial spectrum usually matches the duodenal culture results, according to several studies.^{130,149} Surgical technique (in so far as the choice of a midline vs transverse vs kidney transplant incision) does not affect the rates of intra-abdominal infections as long as the pancreas graft is placed intraperitoneally.^{142,150,151} Interestingly, and in contrast to kidney transplants,¹⁵² the introduction of new, more potent immunosuppressants such as tacrolimus and mycophenolate mofetil (MMF) have not significantly affected the rates of intra-abdominal infections after pancreas transplants either.¹¹ Rather, the introduction of MMF correlated with significant other improvements in the rates of intra-abdominal infections and of the resulting mortality (as discussed above).

Clinical Presentation and Treatment

Nearly all intra-abdominal infections are diagnosed within the first 3 months posttransplant, most within the first 30 days.¹⁰ Fungal infections are diagnosed, on average, somewhat later than bacterial infections.^{6,10} Clinical presentation may range from nonspecific abdominal complaints to diffuse peritonitis, fever, ileus, nausea, vomiting, leukocytosis, hyperglycemia, and sepsis. About 50% of intra-abdominal infections are diffuse and 50% localized (e.g., an abscess).¹⁰ About 30% of intra-abdominal infections are associated with a leak.^{10,147} The most commonly isolated micro-organisms include staphylococcus and enterococcus species, gram-negative bacteria, and *Candida albicans*.^{6,10,130,133,153} In one large retrospective study during the cyclosporine era, 54% of all intra-abdominal infections posttransplant were caused solely by bacterial species, 15% were caused solely by fungal species, and 31% were mixed bacterial and fungal infections.¹⁰

In clinically stable recipients, a workup must characterize the extent and nature of their infection, because treatment depends on the type of infection (e.g., diffuse peritonitis vs a localized abscess). At the same time, graft thrombosis and a leak must be ruled out, irrespective of the drainage method. The study of choice is abdominal CT with oral and IV contrast. For bladder-drained grafts, bladder contrast should be routinely used to rule out a leak. For enteric-drained grafts, bladder contrast does not need to be administered unless a bladder leak from a simultaneously transplanted kidney is clinically suspected. Administration of IV contrast must be adequately timed to allow assessment of pancreas graft perfusion and delineate the extent, if any, of pancreatitis and pancreatic necrosis. If there are any doubts about organ perfusion and viability, a color duplex Doppler ultrasound study is indicated. If a bladder-drained graft recipient still has surgical drains in place, culture of the same micro-organisms from the drainage fluid as from the urine, with a similar resistance pattern on antibiotic sensitivity testing, is virtually diagnostic of an infected bladder leak.

For stable recipients who have a localized intra-abdominal abscess, conservative care with percutaneous catheter drainage is a reasonable first-line treatment option. However, in enteric-drained recipients a leak (which would indicate immediate relaparotomy) must first be ruled out. Similarly, only bladder-drained recipients without a leak, or with a well-controlled small leak (treated concurrently by Foley catheter drainage and a drain in the leak area), are candidates for conservative management. When intra-abdominal fluid collections suggesting an abscess are percutaneously drained, the drain should be left in place until its output has ceased and until at least a preliminary microbiologic culture result report is available. Moreover, such a drain facilitates the diagnosis of an occult leak (enteric or bladder) and a pancreatic fistula. A sinogram may help assess obliteration of the abscess cavity and determine the optimal time for drain removal. In all other instances, relaparotomy and open surgical drainage are safer

options.⁸ Depending on the recipient population, between 10% and 50% of all localized intra-abdominal infections can be successfully treated conservatively with percutaneous catheter drainage.^{10,20}

If conservative treatment fails, or if recipients are clinically unstable, relaparotomy, with open abscess and infection drainage, is mandatory.⁸ With severe intra-abdominal infections, the treatment focus should be switched early from salvaging the graft to saving the recipient's life, with a low threshold for performing a graft pancreatectomy.⁸ The morbidity and mortality rates of intra-abdominal infections are higher and the graft salvage rates relatively low.^{6,8,10} Not surprisingly, graft pancreatectomy rates of up to 70% in recipients undergoing relaparotomy for intra-abdominal infections have been reported.^{6,10}

Irrespective of the treatment approach (nonoperative vs operative), systemic IV antimicrobial coverage, of appropriate intensity and duration (as guided by the culture results, if available), is mandatory.¹⁵⁴ Given the devastating impact of fungal intra-abdominal infections on graft and, even more important, patient survival,⁶ long-term (at least 6 weeks) antifungal treatment should be routine for recipients with fungal peritonitis. Those who also have a component of pancreatitis or peripancreatitis may benefit from the use of fluoroquinolones because high tissue concentrations in inflamed and necrotic pancreatic tissue are obtainable using this class of antibiotics.

Preventing intra-abdominal infections begins with appropriate donor selection; the use of older and obese donors must be reconsidered.^{135,136} Preservation time must be minimized.⁶⁴ Retransplant recipients, older recipients, recipients of segmental grafts, and recipients on dialysis (in particular peritoneal dialysis) at the time of their transplant are at higher risk for intra-abdominal infections and must be monitored carefully.^{10,11,99,130,137–145} In the absence of published prospective randomized studies on the subject (with one exception¹⁵⁵), no specific recommendations regarding a particular perioperative antimicrobial prophylactic regimen can be given.¹⁵⁶ However, based on the available evidence and the author's experience, it seems prudent to administer a broad-spectrum antibiotic agent perioperatively for the first 5 days posttransplant. This broad-spectrum antibiotic agent should be supplemented by antifungal prophylaxis with fluconazole for the first 7 days posttransplant. If the donor duodenal culture results demonstrate the presence of fungi, the duration of the antifungal prophylaxis may need to be extended.

Leaks

Despite over three decades of improvements and refinements of surgical technique, posttransplant leaks remain a clinically significant entity, in particular because they are a risk factor for intra-abdominal infections.^{10,147} In case series of bladder-drained grafts, reported leak rates range from 5% to 18%.^{10,99,100,134,147,157–161} For enteric-drained case series,

leak rates of 4% to 9% have been reported.^{31,35,134} However, if leaks are recognized in a timely fashion and managed appropriately the impact on graft and patient survival in the current era is minimal, in particular for bladder-drained grafts. According to the most recent UNOS pancreas registry report, leaks are now responsible for less than 1% of all graft losses.¹¹

With whole-organ grafts, early leaks occur typically at the duodenovesical or duodenoenteric anastomosis, while late leaks (after 4 weeks posttransplant) arise more frequently from the oversewn or stapled duodenal stumps and duodenal segment ulcers. In a large review of bladder-drained grafts, 36% of all leaks were at the duodenocystostomy site, 28% at one of the duodenal stump sites, and in 36% the exact leak site could not be identified because of conservative treatment or indeterminate diagnostic studies.¹⁵⁷

For clinical, therapeutic, and outcome analysis purposes, differentiating between bladder- and enteric-drained grafts is important. Bladder-drained graft leaks are associated with a lower rate of serious infectious complications and a more benign clinical course. In contrast, recipients of enteric-drained graft leaks tend to develop early peritonitis and sepsis due to spillage of enteric contents. This note of caution is underscored by the (statistically nearly significant) higher rate of graft loss from anastomotic leaks for enteric-drained (vs bladder-drained) grafts in the SPK and PAK categories, per a recent UNOS pancreas registry analysis (SPK, 0.8% enteric vs 0.3%, bladder [$P = 0.088$]; PAK, 1.0% enteric vs 0.0%, bladder [$P = 0.077$]).¹¹

Bladder-Drained Grafts

Leaks can be divided into early and late leaks.^{147,157,160} Early leaks occur within the first 4 weeks posttransplant. For whole-organ grafts, they are related either to the duodenocystostomy itself or, less frequently, to one of the oversewn ends of the graft duodenum. In segmental grafts, the leak is located at the pancreaticocystostomy. Leaks often have a technical cause. Adequate anastomotic technique, using a two-layer technique as indicated, is paramount. Moreover, a two-layered closure technique for the duodenal stumps of whole-organ grafts might minimize duodenal leak rates as well. Longer preservation times, severe reperfusion duodenitis, and poor wound healing in immunosuppressed recipients can be co-risk factors for early leaks.⁶⁴ Recent reports suggest that up to 70% of all long-term diabetics have high intravesical pressures, with or without bladder outlet obstruction^{162,163}; these pressures may also play a role in the pathogenesis of postoperative leaks in bladder-drained pancreas recipients. A rare cause of immediate posttransplant leak of amylase-rich fluid is an unligated common bile duct stump at the superior border of whole-organ pancreas grafts.

In contrast, late leaks (after 4 weeks posttransplant) originate most frequently from the graft duodenum.^{157,160} Typically, they are caused by duodenal ulceration and perforation.^{157,160} In some recipients, the ulceration is due to CMV infection. If no infectious cause can be ascertained, ulceration and perforation may be due to ischemia. Noninfectious perforations occur

most frequently at the antimesenteric proximal duodenal border, which is the most distal area supplied by the inferior pancreaticoduodenal artery.^{157,160,161} (The gastroduodenal artery is routinely ligated in whole-organ pancreas recipients.) A bladder instrumentation complication (e.g., an injury during cystoscopic staple removal, a transcystoscopic pancreas biopsy complication) is a rare cause of a leak. At least one case of duodenal rupture due to rejection and necrosis, presumably due to isolated duodenal rejection (in the absence of pancreas graft rejection), has been reported.^{164,165}

Presenting symptoms of early and late leaks include abdominal pain, abdominal distention, fever, vomiting, decreased urine output, peritonitis, and improvement after placement of a Foley catheter.^{10,147,157} Laboratory tests may demonstrate a rise in serum amylase levels in up to 50% of recipients, a rise in serum creatinine level in up to 33% of recipients, and a decrease in urinary amylase levels in up to 40% of recipients.¹⁵⁷ If the leak occurs early and the recipient still has posttransplant drains in place, the amylase and creatinine levels of the drain fluid may be elevated. Note that bladder-drained recipients may selectively leak amylase-rich fluid if they have a duodenal stump or common bile duct stump leak; drain fluid creatinine and serum creatinine levels may not be affected in such recipients.

During the workup of a bladder leak in SPK recipients, it is important not to focus exclusively on a pancreas-related cause. The differential diagnosis process must also include any early ureteral anastomotic leak of the kidney graft.

A definitive diagnosis can usually be made by an imaging study. But, in one series low-pressure cystography had only a sensitivity of 82%.¹⁵⁷ Computed tomography with retrograde filling of the bladder is more accurate, so it is the imaging modality of choice.^{161,166,167} If a leak is clinically suspected but the CT scan is negative, a low-pressure cystogram or voiding cystourethrogram should be done. Some investigators believe that voiding cystourethrogram is superior to conventional cystography.¹⁶⁰ The diagnosis may also be established using a nuclear medicine ^{99m}Tc voiding cystourethrogram; it was suggested that this test has the highest sensitivity of all imaging modalities.¹⁶⁸ If all studies are negative, but an intra-abdominal fluid collection is demonstrated by ultrasonography or a CT scan in a patient suspected of having a leak, then the fluid collection should be percutaneously aspirated and the fluid amylase and creatinine levels should be determined (as discussed above).

The treatment of leaks of bladder-drained grafts depends on the timing of the leak. Early leaks, in particular if they are small and anastomotic, may be treated by prolonged bladder decompression using Foley catheterization; under those circumstances, percutaneous drainage of all intra-abdominal fluid collections is mandatory. Similar microbiologic culture results from the urine and aspirate are pathognomonic for a leak. This approach is successful in about 30% of all recipients.¹⁵⁷ For most infected leaks and for leaks that persist after a nonoperative treatment attempt, relaparotomy with direct repair is warranted. The adequacy of the repair can be ascertained intraoperatively by filling the bladder with meth-

ylene blue diluted in saline solution. High-volume postoperative leaks, in particular in the presence of peritonitis or massive abdominal distention, require immediate relaparotomy and surgical repair. On occasion, if the leak is due to early duodenal ischemia, early enteric conversion is necessary after resection of the ischemic duodenal area. If most of the duodenum is ischemic and must be resected, the duodenal button technique (which leaves only a rim of about 2 to 3 cm in diameter of duodenal tissue around the papilla of Vater) should be considered.¹³⁹

Late leaks, irrespective of their cause, usually require conversion to enteric drainage.^{99,157,160} If CMV infection can be documented histopathologically or by polymerase chain reaction (PCR) as the cause of duodenal ulceration, a concomitant treatment course with IV ganciclovir is warranted.

Overall rates of graft loss after leaks are relatively low. In one large single-center review of leaks in bladder-drained recipients, 29% were treated conservatively (with a 16% nonoperative treatment failure rate), 57% underwent a primary repair (with a 9% failure rate), and 14% underwent a graft pancreatectomy. Eventually, 17% required conversion to enteric drainage.¹⁵⁷

Enteric-Drained Grafts

Leaks in enteric- vs bladder-drained grafts are a potentially more catastrophic event. Therefore, a high index of suspicion and aggressive workup of any enteric-drained recipient suspected of having a leak are paramount. Prompt and definitive treatment of the underlying pathology, without delay once it is diagnosed, is crucial. Typically, early leaks are anastomotic leaks, most frequently from the duodenojejunostomy. Other duodenal technical complications that can result in early leaks are discussed above (see Bladder-Drained Grafts). If the Roux-en-Y technique was used, leaks of the jejunojejunostomy must also be entertained, although they are rare given the excellent blood supply of the native small bowel. Risk factors for early leaks include, anastomotic tension on the entero-enterostomy, severe reperfusion duodenitis (resulting in a tenuous duodenojejunal anastomosis), and use of steroids and other immunosuppressants. Late leaks are frequently due to duodenal perforation, secondary to infectious or ischemic ulcers (see Bladder-Drained Grafts).

A rare cause of a pancreatic leak (pancreaticocutaneous fistula) is the removal of a pancreatic duct catheter. However, this complication is mostly of historic interest.¹⁶⁹ The insertion of a temporary, externalized catheter into the pancreatic duct of segmental enteric-drained grafts for early postoperative graft monitoring has long been replaced by other techniques.

Clinical symptoms include abdominal pain, peritonitis, ileus, fever, leukocytosis, and hyperamylasemia. The most important diagnostic test is abdominal CT with oral contrast administration. But, even with this imaging modality the leak may be difficult to document. Therefore, if an enteric leak is suspected the threshold for diagnostic relaparotomy must be low in enteric-drained recipients. Treatment of leaking enteric-drained

grafts always mandates surgical reexploration. If the graft duodenum is not compromised, the leaking area is well circumscribed, and there is no diffuse peritonitis, primary repair may be attempted. If the primarily employed technique (at the time of the transplant) was a side-to-side duodenojejunostomy, the creation of a Roux-en-Y loop should be considered to exclude the anastomosis and repair site from the fecal stream. If the duodenum is severely compromised (e.g., because of ischemia) and needs to be resected, graft salvage can still be attempted in selected recipients—but only if there is no generalized peritonitis and the recipient is clinically stable and does not have sepsis. Resection of the pancreatic head and pancreatic duct injection with a polymer may be an option.^{54a} Placement of surgical drains should be routine after such interventions. In the face of systemic sepsis or severe peritonitis, a graft pancreatectomy remains the safest option. In one recent case series, transplant pancreatectomy rate was 55% after duodenal segment leaks of enteric-drained grafts.^{169a} Only rarely should creation of a temporary diverting enterostomy and mucus fistula become necessary (e.g., if primary small-bowel reanastomosis after graft pancreatectomy is too unsafe secondary to severe peritonitis and inflammation).

Graft Pancreatitis, Pancreatic Pseudocysts, and Pancreatic Fistulas

Pancreatitis

Pancreatitis, defined as prolonged posttransplant hyperamylasemia, is observed early posttransplant in up to 35% of all pancreas recipients.¹⁰⁷ Complications of graft pancreatitis include pancreatic abscesses, sterile and infected pancreatic necrosis, peripancreatitis with perigraft infection, pancreatic fistulas, sterile and infected peripancreatic fluid collections, and sterile and infected pseudocysts. In contrast to native pancreatitis, graft pancreatitis is often associated with significant peripancreatitis, even when the pancreas graft is only mildly inflamed. Pancreatitis is significant not only because it is commonly associated with infection¹¹ but also because it is a major risk factor for graft thrombosis—the surgical complication currently causing most technical graft losses.^{63,64,66}

However, determining the true incidence and nature of posttransplant pancreatitis is extremely difficult because of the lack of a uniformly accepted definition. Moreover, there is no classification scheme for graft pancreatitis, such as the Atlanta classification system for native pancreatitis.¹⁷⁰ Pancreatitis is readily apparent intraoperatively. But, its diagnosis remains elusive and vague once the recipient's abdomen is closed and direct visual inspection by the transplant surgeon is no longer possible. Serum markers such as amylase and lipase correlate poorly with the severity of pancreatitis. Other surrogate markers, such as the C-reactive protein (CRP), during the first days after implantation can be helpful for retrospective analysis but may be less useful for following the graft clinically on a day-to-day basis and making real-time clinical decisions.

Pancreatitis is best assessed with modern imaging modalities such as contrast-enhanced CT. However, CT is expensive, too cumbersome to be repeated frequently (e.g., daily) for follow-up, and requires administration of nephrotoxic and potentially allergogenic IV contrast agents. Analyzing the causes and consequences of pancreatitis is also hindered by the fact that a substantial proportion of vascular thromboses, for which ischemia-reperfusion pancreatitis is thought to be a significant risk factor, occur early (i.e., within the first 24 to 48 hours posttransplant).⁷ Thus, little or no time is available to measure serum amylase, lipase, and other parameters. Given the currently available clinical diagnostic means, it is virtually impossible to analyze the impact of pancreatitis on outcome in recipients with early graft loss.⁷

Another difficulty is that pancreatitis is so frequently associated with infection that it is hard to determine which of the two complications arose first. The UNOS pancreas transplant registry reports do not even list pancreatitis as a separate technical failure cause but rather analyze pancreatitis together with infection.¹¹ A recent large, single-center study on surgical outcomes of nearly 600 pancreas transplants did not even list pancreatitis as a cause of surgical complications and technical failures.⁴⁰

Pathogenesis and Etiologies

An important immunologic cause of pancreatic inflammation, acute rejection, is discussed extensively in chapter 11.

Impairment of microcirculation is a significant factor in the development of pancreatitis.^{62,171,172} The ischemia caused by preservation and postreperfusion microcirculatory impairment causes exhaustion of the energy metabolism and tissue acidosis, leading to the development of oxygen-free radicals.¹⁷¹ As a result, the strict compartmentalization necessary for acinar cell integrity (to prevent premature activation of proenzymes) is disturbed. The impaired cell integrity, with an imbalance of proteases and antiproteases caused by hypoxia, can then lead to activation of the lysosomal system, resulting in crinophagy and acinar cellular necrosis.¹⁷¹ Vasoconstriction, intravascular coagulation, and increased endothelial permeability may all result in pancreatic edema, which in turn can impair venous drainage and further worsen microcirculation.^{7,8,10} Thus, although the causes of graft pancreatitis differ from those of native pancreatitis the final pathogenetic pathway leading to pancreatic inflammation and necrosis appears to be similar.

Risk factors for pancreatitis include donor risk factors (hemodynamic instability, vasopressor administration), procurement injury, perfusion injury (excessive amounts of flush volume or perfusion pressure), preservation injury associated with extended preservation times, and reperfusion injury.^{7,8,10,62–64,66}

Clinically, pancreatitis caused by ischemia-reperfusion injury must be distinguished from pancreatitis caused by impaired pancreatic duct outflow and pancreatitis caused by infections. One study suggested that nutrition, alcohol intake,

mental stress, and mechanical transabdominal irritation of the pancreas graft may also cause pancreatitis.¹⁷³ Surprisingly, despite the multitude of medications given to pancreas recipients, drug-induced pancreatitis is rare in this population. Of note, a recent single-center study suggested higher graft pancreatitis rates in recipients treated with sirolimus.^{173a}

After the immediate posttransplant period, the most important cause of pancreatitis during the first few weeks to years posttransplant is temporary or permanent pancreatic duct outflow impairment. Relatively rarely, technical and surgical problems may cause narrowing of the pancreatic duct in both segmental and whole-organ grafts. In segmental grafts, pancreatic duct outflow obstruction may be due to stenosis of the duct-to-urothelium or duct-to-bowel mucosa anastomosis.¹⁷⁴ In whole-organ grafts with a duodenal segment, the minor or major papilla may be compromised by the closing stitches applied to the proximal or distal duodenal end. Or, the culprit may be the duodenocystostomy or duodenoenterostomy on the antimesenteric border if the duodenal circumference is relatively small and the suture bites used to create the anastomosis are relatively large, inverting a significant amount of duodenal wall and narrowing the papillae. Also, several cases of ampullary obstruction due to rejection and postbiopsy edema have been reported.^{174a} Finally, stenosis of the duodenovesical or duodenoenteric anastomosis (due to surgical error or chronic fibrosis) may also on occasion be responsible for pancreatic duct outflow impairment.

Causes of impaired pancreatic duct outflow unique to bladder-drained pancreas grafts include “urinary reflux” in at least 10% of all pancreas recipients and, rarely, vesical or duodenal urolithiasis.^{160,161,175} Note that reflux pancreatitis may be a misnomer. The name suggests that urine refluxing into the pancreatic duct of bladder-drained grafts leads directly to pancreatitis, but this has never been proven conclusively. The true cause may, in fact, be a secretory block caused either by reflux of urine into the pancreatic duct and its ramifications or by high intravesical and high intraduodenal pressures. Such pressures may result from, for example, a neurogenic diabetic bladder or a urinary outflow obstruction, especially in male recipients (see Urologic Complications).^{161–163} Reflux pancreatitis in bladder-drained grafts has been well characterized, but its significance in enteric-drained grafts is unknown. In particular in enteric-drained whole-organ grafts using the side-to-side duodenoenterostomy technique, the pancreatic duct outflow may be intermittently impaired by the recipient’s fecal stream. In bladder-drained recipients, urolithiasis can also cause pancreatic duct outflow obstruction. At least one case report described a stone in the bladder and graft duodenum that formed on the nidus of an intravesically protruding nonabsorbable suture.¹⁷⁵ This rare cause of pancreatitis must be considered if no other cause can be found.

Other relatively rare etiologies of pancreatitis include biopsy complications and bacterial and viral (e.g., CMV) infections.^{175a,175b,176} One case series on pancreas recipients with CMV infection suggested that late intrapancreatic abscesses were more common in recipients with CMV infection.¹⁷⁶

Given the amount of mechanical trauma inflicted on a pancreas during procurement and its manipulation during back-table preparation and implantation, it is surprising that more severe episodes of postreperfusion graft pancreatitis are not seen. Clinically, severe courses of pancreatitis are rare. A partial explanation may be that the transplanted (vs the native) pancreas is intraperitoneally located, allowing absorption of peripancreatic fluid and interaction with the host's peritoneal immune defense system.

Clinical Presentation and Diagnosis

A large proportion of pancreatitis episodes occur early post-transplant and are related to ischemia-reperfusion injury. Importantly, they can be associated with infectious complications. Late pancreatitis, after the first month posttransplant, is more commonly caused by reflux pancreatitis in bladder-drained grafts and CMV infection in bladder- and enteric-drained grafts.

The diagnosis of pancreatitis is based on hyperamylasemia in combination with abdominal pain and tenderness over the pancreas graft. In more severe cases of pancreatitis, the clinical presentation may also include nausea, vomiting, and ileus. Abdominal distention may be caused by pancreatic ascites or ileus secondary to peripancreatic inflammation. In severe cases of graft pancreatitis, recipients may become hemodynamically unstable and even develop an acute respiratory distress syndrome (ARDS). In bladder-drained grafts, the timed urinary amylase output often decreases markedly during pancreatitis episodes. However, the endocrine secretory capacity is often preserved, even in cases of severe pancreatitis, so that hyperglycemia is only an unreliable indicator of pancreatitis. CRP level can be elevated with pancreatitis, but unfortunately it is only a relatively unspecific sign.

Laboratory tests that should be done include amylase, lipase, and CRP. Foley catheter insertion should be part of the diagnostic workup in any bladder-drained recipient with graft pancreatitis. In cases of significant graft pancreatitis, the degree of inflammation and presence of pancreatic necrosis can best be assessed by CT. Appropriately timed administration of the IV CT contrast bolus enables assessment of the viability and perfusion of pancreatic parenchyma. Magnetic resonance imaging (MRI) may be an alternative for selected recipients, especially if peripancreatic fluid collections are to be assessed as well. Other causes of hyperamylasemia (such as rejection, leak, intragraft AVF, true graft aneurysms, and pseudoaneurysms) must be ruled out if no sufficient explanation for hyperamylasemia is found on clinical and imaging studies. Graft biopsy can diagnose CMV pancreatitis by demonstrating histopathologic findings specific for CMV infection (e.g., CMV inclusion bodies).^{175a}

Treatment

Treatment of pancreatitis is dictated by the underlying cause. Of note, the cessation of all oral intake has a similar effect on the pancreas graft and native pancreas.^{177,178} Significant

ischemia-reperfusion pancreatitis is best treated by bowel rest and insertion of a nasogastric tube. On occasion, parenteral nutrition is necessary. However, instituting total parenteral nutrition and stopping enteral feeding has never been conclusively proven to be effective in treating graft pancreatitis. Nevertheless, at least in cases of severe pancreatitis, such a regimen, at least temporarily, is prudent. These conservative measures should suffice, in most cases, to control the symptoms. Other conservative approaches that have been suggested to inhibit pancreatic exocrine secretions (but have never been proven in controlled trials) include atropine, carboxyanhydrase inhibitors, glucagon, calcitonin, H₂ blockers, and octreotide.¹⁷⁸ Recipients with severe hemorrhagic pancreatitis may benefit from having peripancreatic drains inserted, with or without a planned relaparotomy for pancreatic debridement. At the least, a follow-up CT scan with IV contrast should be obtained. All these therapeutic approaches are empirical and have not been tested in prospective randomized studies. In cases of severe graft pancreatitis, especially if associated with refractory inflammation and persistent pancreatic ascites, or with significant and potentially life-threatening systemic complications (e.g., ARDS) and infection, removal of the graft may be the only viable option.

Pancreatic duct obstruction as a result of a surgical mishap is rare but requires a reoperation to address the underlying technical problem.

Reflux pancreatitis in bladder-drained recipients is best treated with insertion of a Foley catheter and serial serum amylase level measurements. Insertion of a Foley catheter is also the diagnostic modality of choice for this problem. A urinary tract infection (UTI), which may cause urinary outflow obstruction, must also be ruled out. Treatment of the UTI may suffice to promote adequate bladder emptying and prevent further reflux pancreatitis episodes.

Repetitive episodes of reflux pancreatitis in bladder-drained graft recipients, especially if outflow obstruction of the urinary tract and a UTI have been ruled out, are best treated by conversion to enteric drainage. In one large series, reflux pancreatitis was the indication for conversion to enteric drainage in 19% of the recipients.²¹

Pancreatic duct obstruction caused by other problems (such as urolithiasis) is addressed by treating the underlying problem, i.e., removing the bladder stone or duodenal stone.¹⁷⁵

Infectious pancreatitis is treated with antiviral agents, as indicated.^{175a,175b} It is self-evident that any peripancreatic infections associated with pancreatitis (e.g., peripancreatic abscesses, infected pseudocysts) mandate appropriate surgical or radiological intervention as well as antimicrobial treatment.

The use of the somatostatin analog octreotide to treat *established* pancreatitis has been attempted. One study reported on the selective use of octreotide in pancreas recipients: The drug was begun at a mean of 29 days posttransplant and given for a mean of 13 days.¹⁰⁷ Nonetheless, 57% of the solitary pancreas recipients in that series lost their grafts to infections and pancreatitis.¹⁰⁷ Clearly, more doubled-blinded, random-

ized prospective trials are necessary before routine use of octreotide can be recommended for recipients with pancreatitis. Octreotide must be carefully considered in this particular patient population because it can diminish graft blood flow, cause glucose intolerance and hyperkalemia, and adversely affect cyclosporine blood levels in recipients on oral cyclosporine.^{179–182}

In the absence of effective therapies for pancreatitis, in particular if it was caused by ischemia-reperfusion injury, prevention is the best option. The key is to choose donors with stable hemodynamics and minimal vasopressor and vasopressin administration requirements. Empiric observations suggest that mannitol, when administered intravenously before and after reperfusion of the pancreas graft, may reduce early graft edema. One small retrospective series suggested that high-dose steroid administration to brain-dead donors may decrease the incidence of postreperfusion pancreatitis and even ameliorate graft thrombosis rates.⁶³ Experimental animal models have suggested that various agents, such as the thromboxane A₂ synthesis inhibitor OKY046^{183,184} and the platelet activated factor inhibitor BN-52021,¹⁸⁵ may favorably influence postreperfusion graft pancreatitis; however, clinical testing has not been done. Calcium channel blocker administration, which has been successful clinically in kidney recipients (by preoperative graft perfusion with diltiazem), may be beneficial in pancreas recipients. In one small retrospective study, the incidence of pancreatitis significantly decreased when calcium channel blockers were administered immediately posttransplant.⁶³ Another single-center report on the prophylactic perioperative use of octreotide, although it involved a limited number of recipients, suggested a favorable impact on pancreatitis and its sequelae.¹⁰⁶ However, before any of these proposed pharmacological interventions can be recommended on a routine basis, prospective randomized trials are necessary.

Impaired microcirculation is one of the main factors in the clinically relevant ischemia-reperfusion pancreatitis.^{7,8,10,171,172} Therefore, several investigators have focused, in experimental small- and large-animal models, on the use of dextran, L-arginine, and N-acetylcysteine to improve postschemic microcirculation.^{186–188} In particular, the role of nitric oxide (NO) in ischemia-reperfusion injury and the development of microcirculatory postreperfusion failure is under intense scrutiny.^{187,189} Nitric oxide has beneficial effects not only by causing vasodilatation and increasing blood flow but also by inhibiting granulocyte adhesion and platelet aggregation. So, it is not surprising that encouraging results have been obtained in animal models with substances that increase NO levels, such as L-arginine and sodium nitroprusside.^{187,189} However, such therapy awaits clinical testing, which may be hampered because the L-arginine and sodium nitroprusside cause systemic hypotension.^{187,189} Further study is needed of the effect on organ donors of desmopressin, a synthetic analogue of the natural hormone vasopressin.⁶² Desmopressin impairs microcirculation by increasing leukocyte adhesion and en-

hancing platelet P-selectin expression.⁶² It also induces endothelial von Willebrand factor release and may adversely affect intrapancreatic coagulation.⁶² Future clinical research on this subject may help determine whether pancreatitis can be prevented by avoiding or minimizing the use of inotropes and desmopressin in brain-dead organ donors.

Pancreatic Pseudocysts

The true incidence of pancreatic pseudocysts is difficult to determine. Not every pancreatic fluid collection documented by posttransplant imaging is a true pseudocyst. Nonabsorbed peripancreatic, peritoneal, or lymphatic fluid collections may be mistaken for pseudocysts.²⁰ Other causes of peripancreatic fluid collections include hematomas and abscesses.²⁰ Peripancreatic fluid collections have been observed in up to 20% of all pancreas recipients.^{5,190,191} Such collections may occur more often in duct-occluded segmental grafts.² The true incidence of symptomatic pseudocysts is probably less than 10%.

From an etiologic and, in particular, therapeutic standpoint, pseudocysts that still have a connection with the pancreatic ductal system must be distinguished from other peripancreatic fluid collections (including pseudocysts) that do not communicate with the pancreatic ductal system.

Clinically, pseudocysts can present with hyperamylasemia, hemorrhage, infection, and local symptoms such as tenderness and distention.

The diagnosis can be established with an imaging modality such as ultrasound, CT, or MRI.^{20,190,191} In general, ultrasonography alone does not exactly delineate the anatomic configuration of pseudocysts. So, before proceeding with therapeutic planning, cross-sectional imaging by CT or MRI is indicated. If imaging results are equivocal (e.g., in the case of a complex pseudocyst with multiple septations and an inhomogeneous appearance), pseudocysts can be differentiated from hematomas or abscesses by determining the amylase in the cyst fluid after cyst aspiration or drainage. Markedly elevated amylase levels are more consistent with a pseudocyst. Aspiration and drainage also permit cyst fluid culturing and may help exclude infections.

Diagnostic imaging must also try to establish whether the pseudocyst is communicating with the main pancreatic duct. If it is, ductal obstruction or, in bladder-drained recipients, repetitive bouts of reflux pancreatitis must be ruled out. Otherwise, the pseudocyst may not be amenable to definitive treatment. The study of choice to demonstrate communication with the pancreatic duct is contrast injection into the cyst cavity through a puncture needle or temporary drain.

The strategy for treating peripancreatic pseudocysts and fluid collections follows several principles. For pseudocysts of the native pancreas, the tendency over the past years has been to intervene therapeutically only if complications develop, such as infections, hemorrhage, or perforation. In fact, an expectant attitude has become the therapeutic mainstay. But, in pancreas recipients this approach must be tempered

somewhat because pseudocysts and other peripancreatic fluid collections may be, or may become, bacterially contaminated. In addition, pancreas recipients are immunosuppressed and as such more prone to develop infectious complications.

All symptomatic and large asymptomatic pseudocysts and peripancreatic fluid collections should, therefore, be aspirated. If there is any doubt about the quality of the cyst fluid, and if an infection cannot be ruled out at the time of the aspiration, it is safe and prudent to leave a catheter in place. The amylase level in the cyst fluid can then be determined, and bacterial and fungal cultures can be obtained. If the main pancreatic duct of the graft communicates with the pseudocyst with preferential exocrine secretion drainage through the cyst cavity into the drainage catheter, additional diagnostic radiological studies must be obtained, such as a contrast injection, to rule out obstruction of the main pancreatic duct. In bladder-drained pancreas recipients, this situation mandates Foley catheter insertion and a cystogram to rule out an obstruction of the duodenocystostomy. Any underlying infection must be treated with appropriate antibiotics. A substantial proportion of pseudocysts and peripancreatic fluid collections will respond to these measures. Percutaneous drainage may be in particular effective for pancreatic pseudocysts that communicate with a normal pancreatic duct and for noninfected and infected noncommunicating pseudocysts and peripancreatic fluid collections. About 50% of all pseudocysts and peripancreatic fluid collections are amenable to this conservative treatment.¹⁹⁰

Treatment other than simple cyst aspiration or drainage (i.e., an operation) is indicated from the outset in case of complications, namely, hemorrhage, cyst perforation, or a symptomatic pseudocyst that is refractory to repetitive nonoperative intervention. Recipients who have a pseudocyst that communicates with a stenotic proximal pancreatic duct should initially undergo a percutaneous catheter placement and then must be considered for a definitive operative drainage procedure. As with native pancreatic pseudocysts, internal drainage is the procedure of choice. For bladder- and enteric-drained grafts, internal drainage may involve creating a cyst jejunostomy.¹⁹² For bladder-drained grafts with cysts in the vicinity of the bladder, percutaneous creation of a cyst-cystostomy has been described as an alternative in at least one pancreas recipient.¹⁹³

Pancreatectomy should only rarely be necessary for pseudocysts that do not respond to the nonoperative and operative treatment outlined above, in particular complicated pseudocysts with infection or major hemorrhage due to erosion of large pancreatic or peripancreatic blood vessels.

Overall, if pseudocysts and peripancreatic fluid collections are managed appropriately, graft and patient survival rates are not affected significantly.

Pancreatic Fistula

Pancreatic fistulas in whole-organ grafts have become rare, occurring in less than 5% of all cases. In contrast, in the early

experience with duct-injected segmental grafts they were observed in as many as 50% of all pancreas recipients.^{2,74,194} In the past, fistulas were also rarely caused by removal of pancreatic duct drainage catheters from segmental pancreas grafts.^{2,169} Currently, in the era of whole-organ pancreas transplants fistulas are most commonly the sequela of pancreatitis, with or without pseudocyst formation. Exocrine secretions from the native pancreas can total about 1.5 L/d; heterotopically transplanted, denervated grafts still produce as much as 700 to 800 mL of pancreatic juice per day.¹⁹⁵

The clinical presentation is obvious, with a fistula draining amylase-rich pancreatic juice.

Diagnostically, a fistulogram obtained by direct injection of the fistula with contrast delineates the anatomy of the fistula and may demonstrate a communication with the pancreatic duct. A fistulogram can also help rule out an obstruction of the main pancreatic duct.^{174,174a} In addition, cross-sectional imaging studies such as CT or MRI are valuable: They can rule out underlying abscesses or infected peripancreatic fluid collections that may perpetuate the fistula and thwart conservative treatment.

Therapeutically, an initial conservative treatment attempt is warranted, including discontinuing all oral intake and beginning total parenteral nutrition. Doing so can reduce the total amount of exocrine secretions of the pancreas graft to about one fourth of normal.^{177,178} Any associated infection must be treated (e.g., percutaneous abscess drainage, appropriate IV antibiotics). In bladder-drained recipients, it is also prudent to insert a Foley catheter to definitively rule out reflux pancreatitis. A number of substances—including H₂ blockers, atropine, carboxyanhydrase inhibitors, glucagon, calcitonin, and enterally administered pancreatic enzymes—can inhibit pancreatic exocrine secretions, but only the somatostatin analog octreotide has a proven clinical effect on the native pancreas.^{177,196,197} Octreotide has also been used in recipients with fistulas posttransplant.^{180–182,198} In at least one recipient, a persistent pancreatic fistula was successfully treated with octreotide and direct injection of fibrin glue into the fistula.⁸² Potential drawbacks of that approach include thromboembolic complications from an inadvertent intravascular fibrin glue injection. Moreover, as discussed above (see Pancreatitis), octreotide has several drawbacks, including cost.^{179–182}

The rare recipient for whom conservative treatment fails must undergo a relaparotomy. Depending on the fistula anatomy and location, and the presence or absence of pancreatic duct outflow obstruction, revision of the pancreaticocystostomy or enterostomy (in case of segmental grafts) or an internal drainage procedure using a limb of defunctionalized small bowel (Roux-en-Y) may be indicated.^{174,199}

Often, treatment of pancreatic fistulas requires a prolonged treatment period and a significant amount of patience on both the surgeon's part and the recipient's part. In rare cases, after failure of all other conservative strategies and, in particular in the face of associated intra-abdominal infections, transplant pancreatectomy may be the only definitive treatment.

Bleeding

Significant intra-abdominal bleeding after pancreas transplants is one of the most frequent indications for a relaparotomy. One large single-center review of transplants during the cyclosporine era reported a relaparotomy incidence of 13% for bleeding.⁸ A more recent case series from the same institution during the tacrolimus era noted that bleeding remained the most common indication for a relaparotomy in 7% of all pancreas recipients.⁴⁰ Fortunately, the overall impact of bleeding on graft survival is comparatively benign. According to the most recent UNOS pancreas registry report, only 0.2% of all pancreas grafts (regardless of recipient category) are currently lost to bleeding.¹¹ In nonuremic PTA recipients and enteric-drained PAK recipients, not even a single graft was lost in the United States over the 4-year period of 1997 through 2000.¹¹

Clinically, it is important to distinguish between intra-abdominal, vesical, and gastrointestinal bleeding.

Intra-Abdominal Bleeding

Early Bleeding

Most significant early posttransplant intra-abdominal bleeding is surgical. It typically derives from the vascular anastomoses or unligated peripancreatic or pancreatic blood vessels. On occasion, diffuse early bleeding may occur from the pancreas graft without any obvious surgical bleeding source. Such bleeding is in particular common if the recipient's coagulatory system is deranged (e.g., after a long transplant procedure in SPK recipients during which large fluid volumes are administered without adequate coagulation factor or platelet substitution, or with vitamin K deficiency).²⁰⁰ A significant proportion of early posttransplant bleeding is caused by perioperative anticoagulation, which is now used by many centers for prophylaxis against thrombosis.^{7,70} However, as discussed earlier (see Vascular Complications), most surgeons would rather return a patient to the operating room for hemostasis and hematoma evacuation than for a graft pancreatectomy secondary to graft thrombosis. In the early postoperative period, it is especially important to include venous pancreas or kidney graft thrombosis in the differential diagnosis of a hemoperitoneum. This is true whenever bleeding from the duodenal segment of whole-organ grafts (i.e., hematuria for bladder-drained grafts and lower gastrointestinal bleeding for enteric-drained grafts) or from the transplant ureter (i.e., hematuria) is observed.

Once bleeding or a significant intra-abdominal hematoma is diagnosed, any underlying abnormality of the coagulation profile should be corrected.²⁰⁰ If the bleeding persists, the recipient should undergo re-exploration. Re-exploration for bleeding must not be delayed because prolonging hemodynamic instability or anemia in recipients with a high incidence of pre-existing coronary artery disease is not warranted from a cardio-

vascular perspective.^{55,56} Moreover, a large hematoma can serve as an ideal agar for bacteria, resulting in an intra-abdominal infection that may have deleterious consequences for graft and patient survival. The evacuation of a hematoma can be therapeutic in itself, even if no surgically correctable bleeding source is identified: The profibrinolytic factors contained in the clot may self-perpetuate diffuse perigraft bleeding.

Most cases of early postoperative intra-abdominal bleeding can be prevented by meticulous back-table preparation of the pancreas, including ligating all peripancreatic tissues and blood vessels.^{7,8}

Late Bleeding

Significant and sometimes life-threatening late intra-abdominal bleeding is rare and can be encountered when the recipient has a freely ruptured mycotic arterial pseudoaneurysm, a ruptured true aneurysm (e.g., of the graft's splenic artery), or a ruptured AVF.^{114,118,122,126} Treatment is directed at the underlying cause (see Vascular Complications). On occasion, in SPK and PAK recipients biopsy complications may cause bleeding but usually does not require operative reintervention.

Vesical Bleeding

The differential diagnosis and treatment for early hematuria are discussed in detail below (see Urologic Complications). Briefly, early posttransplant hematuria is frequent in bladder-drained recipients and is usually self-limiting. In most recipients, the management of early hematuria includes institution of a continuous bladder irrigation regimen. On occasion, cystoscopy may be necessary for hemostasis and bladder clot evacuation. Venous pancreas or kidney graft thrombosis, as well as hyperacute graft rejection, must always be ruled out.

Late hematuria in bladder-drained recipients, if not caused by rare complications such as an AVF or a biopsy complication, is often associated with duodenal complications (e.g., ischemic ulcers, duodenal CMV infection, acute or chronic rejection, chronic exposure to urine).^{157,160} As discussed below (see Urologic Complications), most recipients with substantial late hematuria will eventually require conversion to enteric drainage. Massive bleeding into the bladder due to a ruptured mycotic arterial pseudoaneurysm (in bladder- and enteric-drained recipients) warrants emergent operative reintervention (see Vascular Complications).^{113,118,121}

Gastrointestinal Bleeding

In enteric-drained recipients, early bleeding of the duodenum or suture line presents as lower gastrointestinal bleeding. If it does not respond to conservative measures (e.g., correction of underlying coagulopathy abnormalities or cessation of perioperative anticoagulation),²⁰⁰ operative revision may be indicated in rare circumstances.

For late bleeding that also presents as lower gastrointesti-

nal bleeding in enteric-drained whole-organ recipients, the most common causes are ischemic duodenal ulcers, duodenal CMV infection, acute and chronic duodenal rejection, bleeding from the duodenoenteric anastomosis, and duodenitis.^{200a} Interestingly, late bleeding is observed even in enteric-drained graft duodenal segments—which, unlike their bladder-drained counterparts, do not suffer from chronic unphysiological exposure to urine.^{157,160} In cases of massive lower-gastrointestinal bleeding, from a differential diagnostic standpoint erosion of a mycotic arterial pseudoaneurysm into the recipient's native intestinal system must be considered in both bladder- and enteric-drained recipients.^{114,115,118} Massive bleeding requires expeditious workup (including a CT scan with IV contrast) and emergent reintervention. For nonmassive bleeding, benign or malignant diseases of the recipient's native intestine (in particular colon neoplasms) must be ruled out. Although upper-gastrointestinal ulcers in solid-organ recipients have become rarer with modern immunosuppression,²⁰¹ a gastric or duodenal ulcer must still be ruled out if no lower-gastrointestinal bleeding source can be found. Workup includes colonoscopy: Any demonstration of blood exiting through the ileocecal valve may help localize the bleeding source to the upper-gastrointestinal tract or to an enteric-drained pancreas graft. In an acute situation, a ^{99m}Tc-labeled red blood cell scan may help approximately localize the bleeding source.²⁰²

If the bleeding persists and has been localized to an enteric-drained pancreas graft, a relaparotomy is indicated. For duodenal pathology, partial or subtotal duodenal resection is indicated.^{200a} If so little duodenal tissue is left that not even a duodenal button technique is doable, a pancreas graft may still be salvaged by injecting the pancreatic duct with a polymer, thus converting the enteric-drained graft into a duct-injected graft.^{54a} Recipients who are not amenable to a pan-

creas-sparing operation, as well as recipients with a ruptured mycotic arterial pseudoaneurysm, will require a graft pancreatectomy (see Vascular Complications).^{114,118}

Urologic Complications

It is important to distinguish between complications specifically associated with bladder drainage, those independent of the exocrine secretion drainage method, and those related to a kidney graft (in SPK, PAK, or kidney after pancreas [KAP] recipients). In bladder-drained recipients, urologic complication rates can be as high as 80% depending on the length of follow-up.^{160,161,203–205} In contrast, urologic complication rates in enteric-drained recipients are less than 10%, similar to diabetic KTA recipients (as compared with enteric-drained SPK and PAK recipients) or similar to type 1 diabetics who do not undergo a transplant (as compared with enteric-drained PTA recipients).²⁰⁶

Most urologic complications have no adverse effect on graft and patient survival as long as they are appropriately managed. Yet, as a group, urologic complications are arguably the most frequent indication for posttransplant procedures and operative reinterventions, ranging from percutaneous drainage to cystoscopy to relaparotomy.

Given their surgical relevance, bladder leaks and reflux pancreatitis are discussed in separate sections above.

Urologic Complications in Bladder-Drained Recipients

Hematuria

Hematuria occurs in 11% to 35% of all bladder-drained pancreas recipients and can be divided into two categories: early and late hematuria (Table 9.2.2.2).^{160,161,203–205} Early hema-

TABLE 9.2.2.2. Causes of posttransplant hematuria in bladder-drained pancreas recipients.

Early hematuria (<4 wk posttransplant)	Late hematuria (>4 wk posttransplant)
Anastomotic bleeding (suture or staple line)	Duodenal ulcer (e.g., ischemia, CMV)
Ureteroneocystostomy bleeding (SPK recipients)	Duodenitis (e.g., viral [CMV], bacterial)
Duodenitis (reperfusion injury, rejection)	Acute or chronic rejection (duodenum or pancreas graft)
Foley catheter trauma	Postbiopsy bleeding (pancreas or kidney graft)
Postbiopsy bleeding (pancreas or kidney graft)	UTI
Pancreas graft thrombosis (venous > arterial)	Cystitis (infectious or noninfectious)
Acute pancreas graft rejection	Urethritis
Reflux pancreatitis	Reflux pancreatitis
UTIs	Intragraft AVF (pancreas or kidney graft)
Cystitis (infectious or noninfectious)	Suture line (e.g., staple line bleeding or erosion)
Urethritis	Pancreatic fistula
Intragraft AVF (pancreas or kidney graft)	Mycotic pseudoaneurysm with penetration into the bladder (arteriovesical fistula)
Kidney graft thrombosis (venous > arterial) (SPK recipients)	Bladder ulcer
	Bladder stones
	Bladder and ureteral tumors
	Kidney tumors (native or transplanted kidney)
	Prostatitis
	Benign prostatic hyperplasia
	Prostatic carcinoma

turia occurs within the first 4 weeks posttransplant and late hematuria after 4 weeks.

Early Hematuria

Early hematuria occurs frequently. Usually, it originates from the duodenovesical anastomosis (suture or staple line bleeding). On occasion, early hematuria is caused by reperfusion duodenitis. In most recipients, conservative care will suffice, consisting of insertion of a three-way Foley irrigation catheter, institution of continuous bladder irrigation, and cessation of anticoagulant and antiplatelet agent therapy. For underlying abnormalities of the coagulatory cascade, fresh frozen plasma may be needed.

If bleeding persists despite these measures, cystoscopy may be indicated. At that time, bleeding mucosa or submucosal blood vessels, usually at the duodenovesical anastomosis, can be fulgurated. During the same intervention, any intravesical clot can be evacuated cystoscopically; doing so may have a beneficial effect on hemostasis because it allows the bladder to collapse and contract. In the vast majority of recipients, these measures will control early hematuria, even if it is severe. Some authors have suggested alkalinizing the continuous bladder irrigation solution and administering octreotide as supportive measures.^{161,207} However, such measures have not been tested in a prospective manner, so their clinical effectiveness remains unproven. Relaparotomy for early hematuria should only be necessary under exceptional circumstances.

No significant differences with respect to hematuria were observed in one study comparing hand-sewn vs stapled duodenocystostomies.²⁰⁸ Nonetheless, with stapled duodenocystostomies it is advantageous to oversee all staple lines from the inside of the bladder. A running absorbable monofilament suture should be used. Oversewing will minimize postoperative hematuria and may prevent chronic staple exposure to urine, which could serve as a nidus for bladder stone formation.

Other causes of early hematuria are listed in Table 9.2.2.2. Their treatment is either self-explanatory or discussed elsewhere in this book.

Late Hematuria

In most cases, late hematuria is associated with duodenal pathology. Cystoscopy, the diagnostic study of choice, may reveal duodenal ulcers. They can be the result of acute or chronic duodenal rejection, a duodenal CMV infection, or an ischemic duodenal ulcer.^{157,160,161,165} Exact determination of the cause of a duodenal ulcer may be difficult unless a cystoscopic duodenal biopsy or a histological specimen obtained at reoperation is diagnostic for CMV infection. Ulcers occurring on the antimesenteric duodenal side, in particular at the proximal, postpyloric end, have been postulated to be of ischemic etiology.^{157,160,161} In whole-organ pancreas graft recipients, the gastroduodenal artery is ligated and the blood supply of the proximal duodenum depends on retrograde flow through the inferior pancreaticoduodenal artery and pancreaticoduodenal

arcade.⁷ Some authors have suggested that duodenal ulcers are the result of multiple insults (e.g., preservation, rejection, chronic bladder and duodenal distention from a diabetic bladder, ischemia).¹⁶¹ If the hematuria associated with duodenal ulcers responds neither to symptomatic treatment (continuous bladder irrigation) nor more specific treatment (e.g., IV ganciclovir for CMV-related duodenal ulcers), then direct treatment of the bleeding ulcers by fulguration may be attempted. The risks associated with this approach include duodenal perforation as well as exposure and injury of submucosal blood vessels in the head of the pancreas. The result can be an arterial duodenovesical fistula, in particular with repeated fulgurations.²⁰⁹ Most centers, therefore, prefer conversion to enteric drainage for treatment of duodenal pathology.^{157,160,161}

The differential diagnosis of late hematuria also includes a number of other conditions, including anastomotic suture or staple line bleeding, bladder stones, and cystitis with or without bladder mucosal ulcers.^{160,161,210,211} If the bleeding is associated with a well-circumscribed anastomotic problem, stones, or foreign bodies, it is possible to treat these conditions cystoscopically in most cases.^{161,210,211} In contrast, recipients with severe cystitis and bladder ulcers usually require conversion to enteric drainage for definitive treatment.^{157,160,161}

If none of the aforementioned diagnoses can be made, rare causes of late hematuria that must be entertained include duodenal rejection (acute or chronic, isolated or together with the pancreas),¹⁶⁵ reflux pancreatitis, pancreatic fistula, a tumor of a native or a transplanted kidney, and bladder tumor.^{157,160,161,203–205} This wide array underscores that any recipient with nonresolving, late, chronic hematuria should undergo cystoscopy.¹⁶¹

Vascular complications can also present with hematuria and may become life-threatening if not recognized promptly and treated definitively. If bleeding from the pancreatic duct is observed during cystoscopy, an intrapancreatic AVF (e.g., postbiopsy or from the ligated mesenteric pedicle) must be ruled out by color duplex Doppler ultrasonography.¹²² Most AVF can be treated by percutaneous embolization of the arteriovenous communication.^{112,123–125} Potentially life-threatening arteriovesical fistulas with severe hematuria and hypotension can result from pseudoaneurysms originating from the arterial anastomosis, pancreas graft arteries, recipient's native iliac arteries, or the arterial allopatch left in place after a graft pancreatectomy.^{113,118,121} Most pseudoaneurysms are mycotic and warrant emergent reoperation, revascularization, and a graft pancreatectomy (see Vascular Complications).¹¹⁸

Urethral Complications and Dysuria

The incidence of urethral complications posttransplant ranges from 2% to 12%.^{160,161,204,212–215} Urethral complications comprise a wide spectrum of clinical conditions, including urethritis, dysuria, urethral disruption, development of urethrocutaneous fistulas, and, albeit rarely, even autodigestion of the urethra, the meatus, or the glans penis.^{160,161,204,212–215}

Classically, pancreas recipients with the urethritis–dysuria syndrome have severe burning on urination. Yet, frequently, urine culture results are negative and a bacterial cause cannot be documented. This syndrome occurs most frequently in male recipients within the first year posttransplant.^{160,161,212,213} A significant factor in the development of urethral irritation and inflammation appears to be the pancreatic enzymes in the recipient's urine.^{216,217} Because of the presence of activated trypsin in the urine of pancreas recipients, it has been hypothesized that enterokinase in the brush border of the duodenal mucosa activates the proenzyme trypsinogen and the pancreatic enzyme activation cascade.^{216,217} In addition, other serine proteases (such as plasmin, thrombin, and fibrinolysin) and bacterial enzymes may all also contribute to pancreatic proenzyme activation in the bladder.^{161,216,217}

An important cofactor and a likely prerequisite for the development of severe urethral complications is minor urethral trauma (e.g., from a Foley catheter insertion).²¹³ The activated pancreatic enzymes and urine extravasate and cause significant urethral disruption and, on occasion, even fistula formation.^{213,216} In recipients with urethral disruption, the disruption site is usually located in the bulbous urethra.²¹³ If this complication is suspected based on the clinical findings and the recipient's complaints, a retrograde urethrogram can confirm the diagnosis.

Initial treatment of the urethritis–dysuria syndrome consists of short-term urethral catheterization.^{161,212,213} Suprapubic bladder catheter drainage is only indicated rarely, if ever. Alkalinization of the urine may be used as an adjunct to catheterization.¹⁶¹

Any urethral complication may be further compounded by simultaneous UTI; appropriate treatment of any bacterial UTI is therefore of utmost importance.

For all recipients with recurrent or persistent severe urethritis that does not respond to conservative therapy, and for those with significant urethral complications (such as urethral disruption, urethral strictures, and ulceration or autodigestion of the urethra, urethral meatus, or glans penis), definitive treatment consists of conversion to enteric drainage.^{21,24,160,161,213–215} Some centers advocate early enteric conversion once the diagnosis of urethritis and dysuria is made to prevent late complications (e.g., urethral strictures).^{24,160}

Recurrent UTIs

Urinary tract infections are common in bladder-drained recipients; the reported incidence ranges from 10% to 96%.^{100,160,161,218} Risk factors include instrumentation of the urinary outflow tract (e.g., perioperative Foley catheterization), a high degree of host immunosuppression, bacterial or fungal colonization of the donor duodenal segment, voiding dysfunction due to a ballooning duodenal segment, and increased postvoid residual urine volumes from other causes (such as a diabetic neurogenic bladder). The urinary outflow tract of bladder-drained recipients may be more susceptible

to infection due to the nonphysiological milieu created by the pancreatic secretions; experimentally, it was demonstrated that the urinary trypsin in bladder-drained recipients promotes *in vivo* bacterial adherence to urothelial surfaces, thereby setting the stage for UTIs.²¹⁷

Care of recipients with recurrent UTIs rests on two pillars: First, appropriate antibiotic treatment and prophylaxis (using, if necessary, a rotating antibiotic regimen to prevent emergence of multiresistant microbes) must be instituted; second, an underlying cause of recurrent UTIs must be sought. Postvoid residual urine volumes should be determined to assess bladder function and adequacy of bladder emptying.^{161,205} Recipients may need to undergo cystoscopy to rule out foreign bodies (such as exposed suture material or staples at the duodenocystostomy) and exclude the presence of bladder stones.^{210,211} Cystoscopy allows assessment for benign prostatic hyperplasia and bladder and urethral strictures, all of which may contribute directly or indirectly to recurrent UTIs. If an obstruction with increased postvoid residual urine volumes is suspected, urodynamic testing is indicated.^{160,161} On occasion, a voiding cystourethrogram may be necessary to rule out bladder diverticula or ballooning of the duodenal segment,²¹⁹ which may contribute to high postvoid residual urine volumes.²²⁰

For definitive treatment, removal of any foreign intravesical material (e.g., intravesically exposed suture material or staples, stones) is mandatory.^{210,211} If a specific underlying cause (other than the bladder-drained state) cannot be ascertained, or if a specific, identified problem cannot be addressed cystoscopically, conversion to enteric drainage is indicated.^{21,157,160,161}

Postoperative Voiding Dysfunction and Other Urologic Complications

Among pancreas transplant candidates, the incidence of bladder dysfunction is as high as 43% (as evidenced by abnormal preoperative urodynamics).²²¹ However, despite this relatively high incidence, abnormal preoperative urodynamics do not predict an increased rate of posttransplant urologic complications in bladder-drained recipients.²²¹ Abnormal preoperative urodynamics are therefore not a contraindication to bladder-drained pancreas transplants.^{205,221} In bladder-drained recipients, it is also often impossible to quantify to what degree the voiding dysfunction is due to the bladder drainage procedure (e.g., detrusor dysfunction from surgical trauma and muscular disruption caused by the duodenocystostomy creation, cystitis, urethral inflammation) vs the pre-existing diabetic bladder dysfunction.

Posttransplant voiding dysfunction and recurrent urologic complications should prompt a more detailed workup, including postvoid residual urine volume measurement and peak flow rate determination, in particular in male recipients.^{161,205} If results are abnormal, any underlying pathology (e.g., stricture, benign prostatic hyperplasia) that may be responsible for, or compound, a pre-existing voiding dysfunction

tion (e.g., caused by cystitis and urethral inflammation) must be ruled out and corrected as necessary.^{161,222} A selected subset of recipients with bladder outlet obstruction that does not respond to conservative therapy (e.g., α -blocker therapy, clean intermittent catheterization)^{223,223a} may benefit from cystoscopy and intervention based on cystoscopic findings (e.g., bladder neck incision, limited transurethral resection of the bladder neck).^{161,222} In all other cases of elevated postvoid residual without evidence of obstruction, nonsurgical, conservative treatment options, including intermittent catheterization, must be pursued and optimized.^{161,223} Rarely, conversion to enteric drainage may become necessary.^{223b}

The incidence of lower (but not upper) urinary calculi is higher in bladder-drained recipients as compared with the nontransplant population. Unexplained hematuria or recurrent infections should therefore prompt CT followed by cystoscopy, as necessary, for stone removal.^{210,211}

It is unknown whether long-term exposure of the duodenal mucosa to urine eventually results in neoplastic changes, as seen in nontransplant patients with urinary diversion into an intestinal conduit. In one histopathologic study, only metaplastic (but not neoplastic) mucosal changes were observed in pancreas recipients after up to 6 years of follow-up.²²⁴ In the absence of long-term data, careful workup of recipients who have any symptoms possibly related to duodenal neoplasia (e.g., hematuria) is warranted.

Urologic Complications Independent of the Exocrine Secretion Drainage Method

Postoperative urologic problems not specifically associated with the drainage method should be treated as they would be in diabetic patients who have not undergone a transplant. Urologic diseases and complications that are not primarily related to the transplant operation include diabetic neurogenic bladder dysfunction, benign prostatic hyperplasia, erectile dysfunction, urolithiasis, epididymitis, and, in solitary pancreas recipients, ureteral obstruction of native ureters with or without reflux.^{161,225} Condylomata acuminata as well as benign or malignant tumors of the urothelium, prostate, testes, and kidneys may also develop posttransplant. Such neoplasms must be considered when evaluating a pancreas recipient with new urologic signs and symptoms.

Treatment length and aggressiveness may need to be adjusted in light of the immunosuppressed state of pancreas recipients, in particular regarding infectious complications (e.g., infected penile prostheses) and malignancies.²²⁵ Similarly, screening and surveillance intervals (e.g., after removal of bladder polyps) need to take into account the potentially faster growth characteristics of premalignant or recurring lesions in immunocompromised hosts. In recipients with primary bladder or prostatic malignancies who have a bladder-drained pancreas graft, conversion to enteric drainage at the time of the oncologic operation is usually necessary to facilitate radical and aggressive management of these tumors. Postoperatively, the transplant

team, urologist, and oncologist must closely coordinate the follow-up schedule and any changes in immunosuppression.

Urologic Complications Related to the Kidney Graft

The most common kidney graft ureteral complications in SPK, PAK, or KAP recipients are leaks, stenosis, and obstruction. Such complications occur at a similar frequency as in diabetic KTA recipients; therapeutic strategies are also similar.^{160,204,206}

Small ureteral leaks may be stented (either antegrade or retrograde) in conjunction with prolonged bladder decompression by Foley catheter and urinoma drainage. All other leaks, including those not resolving under conservative treatment, require operative reintervention.

Isolated, short-segment ureteral strictures may be managed nonoperatively by balloon dilatation and stenting. However, if they involve longer or multiple segments and appear to have an ischemic cause, ureteral reimplantation (for distal strictures), or, ureteroureterostomy (between the native and transplant ureter for more proximal strictures), is indicated. Caliceal fistulas are rare and usually occur on the basis of ischemia of the collecting system. They often require surgical correction. The choice of surgical technique depends on the localization and extent of caliceal ischemia and necrosis.²²⁶

Importantly, the differential diagnosis of kidney graft ureteral obstruction after pancreas transplants must also include lymphoceles, even in SPK recipients, whose kidney graft is often placed intraperitoneally. Rapid reperitonealization of the surface of an intraperitoneal kidney graft has led, in several reported cases, to subsequent "extraperitoneal" lymphocele formation and ureteral obstruction.^{160,227}

Prompt recognition and treatment will help maintain the viability and long-term survival of both the kidney and pancreas graft.

Surgical Complications of Conversion from Bladder to Enteric Drainage

Surgical complications after conversion from bladder to enteric drainage have been reviewed in only a few series and are reported to range from 10% to 20%.^{21–26} These complications include postconversion pancreatitis, pancreatic fistulas, duodenal perforation, anastomotic leaks (from the duodenoenterostomy or the Roux-en-Y enteroenterostomy), leaks from the oversewn duodenocystostomy site, and intra-abdominal infections.^{21–26} Also, at least one case of a postconversion enterovesical fistula has been reported.²¹

It is unclear from the available literature whether the use of a loop duodenoenterostomy vs a Roux-en-Y duodenoenterostomy for conversion to enteric drainage has a higher complication rate. With the Roux-en-Y, the number of necessary anastomoses is increased and the complication risk at least hypothetically higher.

Most complications occur early posttransplant, during the hospitalization after the conversion operation.^{21–26} The clin-

ical presentation depends on the underlying pathology and includes fever, nausea, vomiting, abdominal pain, abdominal distention, graft tenderness, peritonitis, ileus, leukocytosis, amylase-rich drainage fluid, and hyperamylasemia. In the largest study on this subject, an increased serum amylase level of >200 mg/dL persisting for more than 4 days postconversion was most indicative of a significant complication.^{21,22} Interestingly, in that study, even if the indication for conversion was reflux pancreatitis, increased postconversion serum amylase levels still indicated a possible complication.^{21,22}

For clinically stable recipients, the diagnostic workup should include a CT scan with oral, IV, and bladder contrast. In clinically unstable recipients with obvious signs and symptoms of peritonitis and sepsis, an immediate relaparotomy is warranted.

Conservative treatment of postconversion pancreatitis consists of stopping all oral intake (with or without institution of a total parenteral nutrition regimen) as well as insertion or maintenance of a nasogastric tube. Such treatment is only indicated for treating pancreatitis in clinically stable recipients as long as there is no evidence of enteric leaks. Minor bladder leaks from the oversewn former duodenocystostomy site can also be treated conservatively with a Foley catheter and, if necessary, percutaneous drainage of the urinoma. In all other cases, surgical re-exploration is mandatory. The choice of surgical procedure is dictated by the intraoperative findings. In the absence of significant local infection and presence of viable bowel, a primary repair of a leak site can be attempted. If there is a well-circumscribed small duodenal necrosis, excision of the necrosis and primary closure may be appropriate. If the primary conversion technique was a loop duodenoenterostomy (side-to-side duodenoenterostomy), strong consideration should be given to converting the side-to-side duodenoenterostomy to a Roux-en-Y duodenoenterostomy to exclude the duodenoenterostomy from the recipient's fecal stream.

If a primary repair, or reanastomosis to the recipient's bowel, is not advisable or feasible, two options may potentially salvage the graft. First, some recipients have undergone exclusion and exteriorization of their graft duodenum, with complete diversion of the exocrine pancreatic secretions into a stoma appliance.^{21,22} In the University of Minnesota experience, exclusion of the graft duodenum to the abdominal wall was a viable alternative and did not increase the risk of graft loss.^{21,22} Second, in at least one recipient the pancreatic duct was ligated, albeit unsuccessfully in the long term because of severe pancreatitis.²² For recipients who are not amenable to any of the aforementioned treatment options, in particular, if faced with diffuse intra-abdominal peritonitis and sepsis, a graft pancreatectomy is warranted. Usually, postoperative drainage of the surgical field should be considered.

For pancreatic fistulas that develop as a sequela of postconversion pancreatitis, an obstruction of the pancreatic duct must be ruled out. Treatment should then proceed as previously discussed (see above).

Synopsis of Recipient and Surgical Technique—Related Risk Factors as Complications

Recipient Category

Technical failure rates for primary transplants are lowest for SPK recipients (7.6%) and higher for posturemic PAK (10.2%) and nonuremic PTA (11.5%) recipients. For primary solitary pancreas (vs SPK) recipients technical failures (from graft thrombosis, infection, pancreatitis, anastomotic leaks, and bleeding) were significantly higher, according to a recent UNOS pancreas transplant registry analysis: 12.2% in the solitary category (PAK, PTA) vs. 8.1% in the SPK category ($P = 0.001$). These differences are mainly explained by the higher graft thrombosis incidence in enteric-drained PAK and PTA recipients. In contrast, a large center recently reported higher relaparotomy and surgical complication rates for SPK (vs PAK recipients).³⁹ But, those higher rates for SPK recipients have not been observed in the UNOS pancreas registry database or by other centers.¹¹ Therefore, this finding likely represents a center effect involving donor and recipient selection.

For SPK grafts, longer preservation time has an adverse impact on the incidence of technical complications and failures (e.g., thromboses and leaks), but for PAK and PTA grafts no such adverse effect of preservation times can be discerned according to the UNOS pancreas registry analysis.^{11,64} The fact that prolonged preservation time is slightly detrimental for SPK but not for PAK and PTA grafts may reflect a more conservative approach to donor selection for solitary pancreas recipients.¹¹ A donor pancreas that has undergone prolonged preservation should be used only if all other donor factors that potentially affect surgical complication rates are favorable.

The recipient's uremic state has no obvious positive impact on the incidence of pancreas graft losses due to graft thrombosis.⁷ However, recipients who are on dialysis at the time of their transplant, in particular peritoneal dialysis, have a higher risk of intra-abdominal infection.^{83,137,138,141}

Finally, a unique vascular complication observed only in SPK recipients is vascular pedicle torsion of intraperitoneally transplanted kidney grafts.^{127,128}

Overall, despite significant progress surgical morbidity remains relatively high, with relaparotomy rates as high as 50% in current case series.^{37,39,41,228}

Transplant Number

In retransplant recipients, surgical complications (such as bleeding and vascular thrombosis) are more common as compared with primary transplant recipients.^{11,229} In a recent UNOS registry analysis, the lower overall graft survival rate for SPK retransplant recipients was mainly due to a higher incidence (21%) of technical failures (vs 8% for primary grafts).¹¹ For PTA recipients, the technical failure rate was also higher for retransplant recipients (19%) than for primary transplant recipients (14%).¹¹ In contrast, the moderate differences in overall graft survival rate observed for PAK retransplant vs primary trans-

plant recipients was mainly attributable to a higher rejection loss rate; the technical failure rate was nearly identical (13% retransplant, vs 11% primary transplant). The higher incidence of technical failures after retransplantation, in particular in the SPK and PTA categories, must be taken into account when selecting donors and recipients for retransplantation.

Duct Management

Bladder and Enteric Drainage

Historically, enteric drainage was associated with higher infection and technical failure rates than bladder drainage.^{4,5,229a} But, these differences have all but vanished over the past half-decade, at least for SPK recipients.¹¹ In contrast, for enteric-drained (vs bladder-drained) PAK and PTA recipients graft thrombosis rates were significantly higher according to a recent UNOS pancreas registry analysis¹¹: in the PAK category, 4.9% for bladder-drained vs. 11.5% for enteric-drained grafts ($P = 0.006$); in the PTA category, 3.5% for bladder-drained vs 14.9% for enteric-drained grafts ($P = 0.004$). Interestingly, the incidence of graft loss from late thrombosis (>1 month posttransplant) was also higher for enteric-drained grafts in both the PAK and PTA categories. It is possible that some of these graft failures thought to be primarily technical are actually from thrombosis secondary to rejection. In enteric-drained PAK and PTA grafts, neither serum creatinine nor urinary amylase can be used to detect a decrease in graft function from rejection before secondary thrombosis. This hypothesis was corroborated by a recently published study on histopathologic findings in grafts that were explanted due to thrombosis within 6 months posttransplant for "graft thrombosis."⁷¹ In that study, acute rejection was observed in at least one third of all thrombosed grafts.⁷¹

The incidence of graft loss from infection, pancreatitis, and bleeding is not different for bladder-drained vs enteric-drained SPK, PAK, and PTA recipients. Although reported leak rates are lower for enteric-drained^{31,35,134} vs bladder-drained grafts,^{10,99,100,134,147,157–161} the incidence of graft loss from anastomotic leakage is higher for primary enteric-drained grafts in the SPK and PAK categories, reaching almost statistical significance (enteric drained vs bladder drained, 0.8% vs 0.3% for SPK ($P = 0.088$), 0.0% vs 1.0% ($P = 0.077$) for PAK, and 0.0% vs 0.0% for PTA recipients). Also, failed pancreas grafts with enteric drainage may require more frequently transplant pancreatectomy.¹⁰²

Surgical enteric drainage technique (with vs without Roux-Y) did not affect technical failure rates.¹¹

The recently proposed venting jejunostomy technique (for monitoring enteric-drained pancreas grafts) is potentially associated with a higher rate of surgical complications, namely, leaks. Multiple anastomoses, as well as a jejunostomy, need to be created and are potential leakage sources.²³⁰

Finally, bladder-drained recipients experience a relatively high incidence of metabolic, pancreatic, and urologic complications, requiring conversion to enteric drainage in about 15% of all cases.^{21–25,231}

Duct Injection

Duct injection with a polymer is now mostly of historic interest. It was associated with a higher incidence of posttransplant pancreatitis, pseudocysts, and pancreatic fistula formation than any other technique.^{2,74,194} Long-term results of duct-injected segmental pancreas transplants suggest an adverse effect of the surgically induced fibrosis of the exocrine pancreatic tissue on the endocrine tissue and its long-term function.^{2,74,110,194} The fibrotic process within the pancreas gland may also lead to long-term involvement of the pancreatic vasculature, resulting in atherosclerotic, occlusive arterial lesions.¹¹⁰

Vascular Management

Vascular management (i.e., portal vs systemic drainage of the venous pancreas graft effluent) does not have a statistically significant impact on technical failures of primary pancreas grafts according to the UNOS pancreas registry analysis covering the period from January 1, 1997, through October 10, 2001.¹¹

Graft Size

Overwhelming evidence from the literature shows that whole-organ (vs segmental) grafts have a more favorable surgical complication profile. Even in the current era, segmental grafts are plagued by higher rates of leaks and intra-abdominal infections with subsequent graft loss.^{73,140,232} Also, graft thrombosis rates remain higher in segmental (vs whole-organ) grafts, even with the use of perioperative antithrombotic prophylaxis.^{73,140,232} Still, the benefits of a segmental pancreas transplant, now usually from a living donor, must be weighed against a 10% to 20% rate of thrombosis and 20% to 25% rate of intra-abdominal infections.^{73,140,232}

References

1. Sutherland DER, Moudry KC. Report of the International Pancreas Transplant Registry. In: Terasaki PI, ed. *Clinical Transplants 1987*. Los Angeles: UCLA Tissue Typing Laboratory; 1988:63–101.
2. Groth CG. Surgical complications following pancreatic transplantation. In: Groth CG, ed. *Pancreatic Transplantation*. Philadelphia: Saunders; 1988:219–238.
3. Groth CG. A critical appraisal of surgical techniques used for pancreatic transplantation. In: Groth CG, ed. *Pancreatic Transplantation*. Philadelphia: Saunders; 1988:191–208.
4. Prieto M, Sutherland DER, Goetz FC, et al. Pancreas transplant results according to the technique of duct management: Bladder versus enteric drainage. *Surgery* 1987;102:680–691.
5. Hesse UJ, Sutherland DER, Najarian JS, et al. Intra-abdominal infections in pancreas transplant recipients. *Ann Surg* 1986;203:153–162.
6. Benedetti E, Gruessner AC, Troppmann C, et al. Intra-abdominal fungal infections after pancreatic transplantation: Inci-

- dence, treatment, and outcome. *J Am Coll Surg* 1996;183:307–316.
7. Troppmann C, Gruessner AC, Benedetti E, et al. Vascular graft thrombosis after pancreatic transplantation: Univariate and multivariate operative and nonoperative risk factor analysis. *J Am Coll Surg* 1996;182:285–316.
 8. Troppmann C, Gruessner AC, Dunn DL, et al. Surgical complications requiring early relaparotomy after pancreas transplantation. *Ann Surg* 1998;227:255–268.
 9. Troppmann C, Gruessner RWG, Dunn DL, et al. Is transplant pancreatectomy after graft failure necessary? *Transplant Proc* 1994;26:455.
 10. Gruessner RWG, Sutherland ER, Troppmann C, Benedetti E, Hakim N, Dunn DL, Gruessner AC. The surgical risk of pancreas transplantation in the cyclosporine era: An overview. *J Am Coll Surg* 1997;185:128–144.
 11. Gruessner AC, Sutherland DER. Analysis of United States (US) and non-US pancreas transplants reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of October 2001. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants 2001*. Los Angeles: UCLA Tissue Typing Laboratory; 2002:41–72.
 12. Davis DJ, MacAulay MA, MacDonald AS, Estabrooks BL. Islets of Langerhans in dog pancreas. Volume fraction and relative distribution of diameters. *Transplantation* 1988;45:1099–1103.
 13. Kelly WD, Lillehei RC, Merkel FK, et al. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery* 1967;61:827–837.
 14. Lillehei RC, Simmons RL, Najarian JS, et al. Pancreaticoduodenal allotransplantation: Experimental and clinical experience. *Ann Surg* 1970;172:405–436.
 15. Gliedman ML, Gold M, Whittaker J, et al. Pancreatic duct to ureter anastomosis for exocrine drainage in pancreatic transplantation. *Am J Surg* 1973;125:245–252.
 16. Dubernard JM, Traeger J, Neyra P, Touraine JL, Tranchant D, Blanc-Brunat N. A new method of preparation of segmental pancreatic grafts for transplantation: Trials in dogs and in man. *Surgery* 1978;84:633–639.
 17. Sollinger HW, Cook K, Kamps D, et al. Clinical and experimental experience with pancreaticocystostomy for exocrine pancreatic drainage in pancreas transplantation. *Transplant Proc* 1984;16:749–751.
 18. Sollinger HW, Kalayoglu M, Hoffman MH, et al. Experience with pancreaticocystostomy in 24 consecutive pancreas transplants. *Transplant Proc* 1985;17(suppl 2):141–143.
 19. Nghiem DD, Corry RJ. Technique of simultaneous renal pancreatoduodenal transplantation with urinary drainage of pancreatic secretion. *Am J Surg* 1987;153:405–406.
 20. Letourneau JG, Hunter DW, Crass JR, et al. Percutaneous aspiration and drainage of abdominal fluid collections after pancreatic transplantation. *AJR* 1988;150:805–809.
 21. West M, Gruessner AC, Metrakos P, et al. Conversion from bladder to enteric drainage after pancreaticoduodenal transplantations. *Surgery* 1998;124:883–893.
 22. West M, Gruessner AC, Sutherland DER, et al. Surgical complications after conversion from bladder to enteric drainage in pancreaticoduodenal transplantation. *Transplant Proc* 1998;30:438–439.
 23. Sindhi R, Stratta RJ, Lowell JA, Sudan D, Cushing KA, Castaldo P, Jerius JT. Experience with enteric conversion after pancreatic transplantation with bladder drainage. *J Am Coll Surg* 1997;184:281–289.
 24. Ploeg RJ, Eckhoff DE, D'Alessandro AM, Stegall MD, Knechtle SJ, Pirsch JD, Sollinger HW, Belzer FO. Urological complications and enteric conversion after pancreas transplantation with bladder drainage. *Transplant Proc* 1994;26:458–459.
 25. Sollinger HW, Sasaki TM, D'Alessandro AM, Knechtle SJ, Pirsch JD, Kalayoglu M, Belzer FO. Indications for enteric conversion after pancreas transplantation with bladder drainage. *Surgery* 1992;112:842–846.
 26. Gaber AO, Shokouh-Amiri MH, Hathaway DK, Hammontree L, Kitabchi AE, Gaber LW, Saad MF, Britt LG. Results of pancreas transplantation with portal venous and enteric drainage. *Ann Surg* 1995;221:613–624.
 27. Rosenlof LK, Earnhardt RC, Pruett TL, Stevenson WC, Douglas MT, Cornett GC, Hanks JB. Pancreas transplantation. An initial experience with systemic and portal drainage of pancreatic allografts. *Ann Surg* 1992;21:586–597.
 28. Newell KA, Bruce DS, Cronin DC, et al. Comparison of pancreas transplantation with portal venous and enteric exocrine drainage to the standard technique utilizing bladder drainage of exocrine secretions. *Transplantation* 1996;62:1353–1374.
 29. Stratta RJ, Shokouh-Amiri HM, Egidi MF, et al. A prospective comparison of simultaneous kidney–pancreas transplantation with systemic–enteric versus portal–enteric drainage. *Ann Surg* 2001;233:740–751.
 30. Douzdjian V, Rajagopalan R. Primary enteric drainage of the pancreas allograft revisited. *J Am Coll Surg* 1997;185:487–492.
 31. Pearson TC, Santamaria PJ, Routenberg KL, et al. Drainage of the exocrine pancreas in clinical transplantation: Comparison of bladder versus enteric drainage in a consecutive series. *Clin Transplant* 1997;11:201–205.
 32. Cattral MS, Bigam DL, Hemming AW, et al. Portal venous and enteric exocrine drainage versus systemic venous and bladder exocrine drainage of pancreas grafts. Clinical outcome of 40 consecutive transplant recipients. *Ann Surg* 2000;232:688–695.
 33. Gruessner AC, Sutherland DER, Gruessner RWG. Enteric versus bladder drainage for solitary pancreas transplants—a registry report. *Transplant Proc* 2001;33:1678–1680.
 34. Kuo PC, Johnson LB, Schweitzer EJ, Bartlett ST. Simultaneous pancreas/kidney transplantation—a comparison of enteric and bladder drainage of exocrine pancreatic secretions. *Transplantation* 1997;63:238–243.
 35. Reddy KS, Stratta RJ, Shokouh-Amiri MH, et al. Surgical complications after pancreas transplantation with portal–enteric drainage. *J Am Coll Surg* 1999;189:305–313.
 36. Freise CE, Narumi S, Stock PG, et al. Simultaneous pancreas–kidney transplantation: An overview of indications, complications, and outcomes. *West J Med* 1999;170:11–18.
 37. Odorico JS, Becker YT, Groshek M, et al. Improved solitary pancreas transplant graft survival in the modern immunosuppressive era. *Cell Transplant* 2000;9:919–927.
 38. Humar A, Harmon J, Gruessner A, et al. Surgical complications requiring early relaparotomy after pancreas transplantation: Comparison of the cyclosporine and FK 506 eras. *Transplant Proc* 1999;31:606–607.
 39. Humar A, Ramcharan T, Kandaswamy R, et al. Pancreas after kidney transplants. *Am J Surg* 2001;182:155–161.
 40. Humar A, Kandaswamy R, Granger D, et al. Decreased surgi-

- cal risks of pancreas transplantation in the modern era. *Ann Surg* 2000;231:269–275.
41. Farney AC, Cho E, Schweitzer EJ, et al. Simultaneous cadaver pancreas living-donor kidney transplantation: A new approach for the type 1 diabetic uremic patient. *Ann Surg* 2000;232:696–703.
 42. Marsh CL, Perkins JD, Sutherland DE, Corry RJ, Sterioff S. Combined hepatic and pancreaticoduodenal procurement for transplantation. *Surg Gynecol Obstet* 1989;168:254–258.
 43. Troppmann C, Pirenne J, Perez RV, Gruessner RWG. The unrecognized posterior gastric artery: A potential cause for surgical complications in pancreas transplantation. *Clin Transplant* Submitted.
 44. Bechstein WO, Reed AI, Sollinger HW. Alternative technique of pancreas graft arterialization. *Clin Transplant* 1992;6:67–68.
 45. Han DJ. Reconstruction of the gastroduodenal artery in pancreatic transplantation. *Transplant Proc* 1996;28:1727–1728.
 46. Nghiem DD. Role of bench angiography in the assessment of pancreaticoduodenal graft blood supply. *Transplant Proc* 1998;30:256.
 47. Nghiem DD. A technique for vascular reconstruction of pancreaticoduodenal allograft. A literature review and case report. *Transplant Int* 1995;8:411–413.
 48. Mizrahi S, Boudreaux JP, Hayes DH, et al. Modified vascular reconstruction for pancreaticoduodenal allograft. *Surg Gynecol Obstet* 1993;177:89–90.
 49. Nghiem DD. Arterialization of portal conduit in pancreas transplantation. *Transplant Int* 2001;14:58–59.
 50. Sutherland DER, Ascher NL. Distal pancreas donation from a living relative. In: Simmons RL, Finch ME, Ascher NL, Najarian JS, eds. *Manual of Vascular Access, Organ Donation, and Transplantation*. New York: Springer-Verlag; 1984:153–164.
 51. Benedetti E, Baraniewski HM, Asolati M, et al. Iliac reconstruction with arterial allograft during pancreas–kidney transplantation. *Clin Transplant* 1997;11:459–462.
 - 51a. Woo EY, Milner R, Brayman KL, Fairman RM. Successful PTA and stenting for acute iliac arterial injury following pancreas transplantation. *Am J Transplant* 2003;3:85–87.
 52. Sutherland DE, Goetz FC, Moudry KC, Abouna GM, Najarian JS. Use of recipient mesenteric vessels for revascularization of segmental pancreas grafts: Technical and metabolic considerations. *Transplant Proc* 1987;19:2300–2304.
 53. Romagnoli J, Papalois VE, Haritopoulos KN, Hakim NS. Successful partial transplant pancreatectomy with end-to-side duct-to-ureter anastomosis: Salvage of a pancreatic allograft. *Int Surg* 2001;86:39–41.
 54. Gautam A, Chakrabarti P, Shapiro R, et al. Techniques for intra-operative surgical problems associated with pancreas transplantation. *Acta Chir Austriaca* 2001;33(suppl 74):19.
 - 54a. Orsenigo E, Cristallo M, Soccì C, et al. Successful surgical salvage of pancreas allograft. *Transplantation* 2003;75:233–236.
 55. Lin K, Stewart D, Cooper S, et al. Pre-transplant cardiac testing for kidney–pancreas transplant candidates and association with cardiac outcomes. *Clin Transplant* 2001;15:269–275.
 56. Mistry BM, Bastani B, Solomon H, et al. Prognostic value of dipyridamole thallium-201 screening to minimize perioperative cardiac complications in diabetes undergoing kidney or kidney–pancreas transplantation. *Clin Transplant* 1998;2:130–135.
 57. Mazza E, DeGasperi A, Corti A, et al. Hypotension after pancreatic reperfusion during combined kidney–pancreas transplantation. *Transplant Proc* 1998;30:265–266.
 58. Corry RJ, Nghiem DD, Schulak JA, Beutel WD, Gonwa TA. Surgical treatment of diabetic nephropathy with simultaneous pancreatic duodenal and renal transplantation. *Surg Gynecol Obstet* 1986;162:547–555.
 59. Sutherland DE, Moudry-Munns KC. International pancreas transplantation registry analysis. *Transplant Proc* 1990;22:571–574.
 60. Sutherland DER, Moudry-Munns KC, Gillingham K. Pancreas transplantation: Report from the international registry and a preliminary analysis of United States results from the new United Network for Organ Sharing (UNOS) Registry. In: Terasaki PI, Cecka JM, eds. *Clinical Transplants 1989*. Los Angeles: UCLA Tissue Typing Laboratory; 1990:19–43.
 61. Gruessner RWG, Dunn DL, Gruessner AC, et al. Recipient risk factors have an impact on technical failure and patient and graft survival rates in bladder-drained pancreas transplants. *Transplantation* 1994;57:1598–1606.
 62. Keck T, Banafsche R, Werner J, et al. Desmopressin impairs microcirculation in donor pancreas and early graft function after experimental pancreas transplantation. *Transplantation* 2001;72:202–209.
 63. Grewal HP, Garland L, Novak K, et al. Risk factors for postimplantation pancreatitis and pancreatic thrombosis in pancreas transplant recipients. *Transplantation* 1993;56:609–612.
 64. Humar A, Kandaswamy R, Drangstveit MB, et al. Prolonged preservation increases surgical complications after pancreas transplants. *Surgery* 2000;127:545–551.
 65. Sutherland DER, Moudry-Munns K, Gruessner A. Pancreas preservation. In: Collins G, Dubernard J-M, Land W, Persijn G, eds. *Procurement and Preservation of Vascularized Organs*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1997:181–191.
 66. Tydén G, Wilczek H, Lundgren G, Ostman J, Gunnarsson R, Jaremko G, Groth CG. Experience with 21 intraperitoneal segmental pancreatic transplants with enteric or gastric exocrine diversion in humans. *Transplant Proc* 1985;1:331–335.
 67. Higgins RM, Gray DWR, Morris PJ. Association of thrombosis after renal transplantation with elevation of the platelet count. *Transplantation* 1995;59:1353–1355.
 68. Reissell E, Lalla M, Hockerstedt K, Lindgren L. Coagulation abnormalities in diabetic patients undergoing renal transplantation. *Ann Chir Gynaecol* 1994;83:251–255.
 69. Burke GW III, Ciancio G, Figueiro J, et al. Can graft loss from pancreas transplant thrombosis be prevented? Thromboelastogram directed anticoagulation for simultaneous pancreas/kidney hypercoagulable state. *Acta Chir Austriaca* 2001;33(suppl 174):2.
 70. Kandaswamy R, Humar A, Gruessner AC, et al. Vascular graft thrombosis after pancreas transplantation: Comparison of the FK 506 and cyclosporine eras. *Transplant Proc* 1999;31:602–603.
 71. Drachenberg CB, Papadimitriou JC, Farney A, et al. Pancreas transplantation: The histologic morphology of graft loss and clinical correlations. *Transplantation* 2001;71:1784–1791.
 72. Ojo A, Hanson J, Wolfe R, et al. Dialysis modality and the risk of allograft thrombosis in adult renal transplant recipients. *Kidney Int* 1999;55:1952–1960.
 - 72a. Wullstein C, Woeste G, Zapletal C, et al. Simultaneous pancreas–kidney transplantation in patients with antiphospholipid syndrome. *Transplantation* 2003;75:562–563.
 73. Humar A, Gruessner RWG, Sutherland DER. Living related donor pancreas and pancreas–kidney transplantation. *Br Med Bull* 1997;53:879–891.

74. Castoldi R, Staudacher C, Ferrari G, et al. Early postoperative surgical complications: Comparison of segmental duct-injected versus whole bladder-drained pancreas transplantation. *Transplant Proc* 1992;24:817–820.
- 74a. Tydén G, Calissendorff B, Billing H, et al. The vascular supply in human pancreaticoduodenal grafts: An angiographic study. *Transplantation Proc* 1990;22:593.
75. Gruessner RWG. Personal communication; November 2002.
- 75a. Gruessner RWG, Sutherland DER, Kandaswamy R, et al. Left-sided pancreas graft placement: Surgical risk or surgical standard? *Am J Transplant* 2003;2(suppl 5):292.
76. Wright FH, Wright C, Ames SA, et al. Pancreatic allograft thrombosis: Donor and retrieval factors and early postperfusion graft function. *Transplant Proc* 1990;22:439–441.
77. Vanrenterghem Y, Roels L, Lerut T, Gruwez J, Michielsen P, Gressese P, Deckmyn H, Colucci M, Arnout J, Vermynen J. Thromboembolic complications and haemostatic changes in cyclosporine-treated cadaveric kidney allograft recipients. *Lancet* 1985;1(8436):999–1002.
78. Mackie IJ, Blewitt S, Clarke P, et al. The effects of long-term cyclosporin A therapy postrenal transplantation on haemostasis. *Br J Haematol* 1986;64:812–813.
79. Neild GH, Reuben R, Hartley RB, Cameron JS. Glomerular thrombi in renal allografts associated with cyclosporine treatment. *J Clin Pathol* 1985;38:253–258.
80. Neild GH, Rocchi G, Imberti L, Fumagalli F, Brown Z, Remuzzi G, Williams DG. Effect of cyclosporin A on prostacyclin synthesis by vascular tissue. *Thromb Res* 1983;32:373–379.
81. Perico N, Remuzzi G. Thromboembolic complications during cyclosporin A therapy: Possible causes and incidence. In: Remuzzi G, Rossi EC, eds. *Haemostasis and the Kidney*. London: Butterworth & Co.; 1989:321–330.
82. Odor-Morales A, Lopez RM, Varela G, Ponce J, Luque E, Chavira SC, Larriva J. Increased thromboxane production by the pancreas after 24-hour preservation in UW-1 solution. *Transplant Proc* 1991;23:1643–1644.
83. Bechstein WO, Malaise J, Sandek F, et al. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in primary simultaneous pancreas-kidney transplantation: One year results of a large multicentre trial. *Transplantation* 2003, in press.
84. Ciancio G, Cespedes M, Olson L, et al. Partial venous thrombosis of the pancreatic allograft after simultaneous pancreas–kidney transplantation. *Clin Transplant* 2000;14:464–471.
85. Corry RJ, Egidi MF, Shapiro R, Sugitani A, Gritsch HA, Jordan ML, Dodson SF, Vivas CA, Scantlebury VP, Rao AS, Fung JJ, Starzl TE. Tacrolimus without antilymphocyte induction therapy prevents pancreas loss from rejection in 123 consecutive patients. *Transplant Proc* 1998;30:521.
86. Wiesner R, Klintmalm G, McDiarmid S, Neuhaus P, Rapamune Liver Transplant Study Group. Sirolimus decreases acute rejection rates in de novo orthotopic liver transplant recipients. *Liver Transplant* 2002;8(suppl):C-16.
87. Nghiem DD. Pancreatic allograft thrombosis: Diagnostic and therapeutic importance of splenic venous flow velocity. *Clin Transplant* 1995;9:390–395.
88. Pozniak MA, Propeck PA, Kelcz F, et al. Imaging of pancreas transplants. *Radiol Clin North Am* 1995;33:581–594.
89. Krebs TL, Daly B, Wong JJ, et al. Vascular complications of pancreatic transplantation: MR evaluation. *Radiology* 1995;196:793–798.
90. Eubank WB, Schmiedl UP, Levy AE, et al. Venous thrombosis and occlusion after pancreas transplantation: Evaluation with breath-hold gadolinium-enhanced three dimensional MR imaging. *AJR* 2000;175:381–385.
91. Douzdjian V, Abecassis MM, Cooper JL, Argibay PF, Smith JL, Corry RJ. Pancreas transplant salvage after acute venous thrombosis. *Transplantation* 1993;6:222–223.
92. Ciancio G, Julian JF, Fernandez L, et al. Successful surgical salvage of pancreas allografts after complete venous thrombosis. *Transplantation* 2000;70:126–131.
93. Gilabert R, Fernandez-Cruz L, Real MI, Ricart MJ, Astudillo E, Montana X. Treatment and outcome of pancreatic venous graft thrombosis after kidney–pancreas transplantation. *Br J Surg* 2002;89:355–360.
94. MacMillan N, Fernandez-Cruz L, Ricart MJ, et al. Venous graft thrombosis in clinical pancreas transplantation: Options for a rescue treatment. *Transplant Proc* 1998;30:425–426.
95. Kuo PC, Wong J, Schweitzer EJ, et al. Outcome after splenic vein thrombosis in the pancreas allograft. *Transplantation* 1997;64:933–935.
96. Ciancio G, Lo Monte A, Julian JF, et al. Vascular complications following bladder drained, simultaneous pancreas–kidney transplantation: The University of Miami experience. *Transplant Int* 2000;13(suppl 1):S187–S190.
97. Schaapherder AFM, van Oosterhout ECAA, Bode PJ, et al. Pancreatic graft survival after arterial thrombosis in simultaneous renal–pancreatic transplantation. *Clin Transplant* 1993;7:37–42.
98. Elkhammas EA, Henry ML, Tesi RJ, Ferguson RM. Combined kidney/pancreas transplantation at the Ohio State University Hospitals. In: Terasaki PI, Cecka JM, eds. *Clinical Transplants* 1992. Los Angeles: UCLA Tissue Typing Laboratory, 1993: 191–197.
99. Douzdjian V, Abecassis MM, Cooper JL, et al. Incidence, management and significance of surgical complications after pancreatic transplantation. *Surg Gynecol Obstet* 1993;451–456.
100. Ozaki CF, Stratta RJ, Taylor RJ, et al. Surgical complications in solitary pancreas and combined pancreas–kidney transplantations. *Am J Surg* 1992;164:546–551.
101. Stratta RJ. Experience with allograft pancreatectomy after pancreas transplantation. *Transplant Proc* 1998;30:443.
102. Stratta RJ, Gaber AO, Shokouh-Amiri MH, Reddy KS, Egidi MF, Grewal HP. Allograft pancreatectomy after pancreas transplantation with systemic-bladder versus portal-enteric drainage. *Clin Transplant* 1999;13:465–472.
103. Sansalone CV, Aseni P, Follini ML, et al. Early pancreas retransplantation for vascular thrombosis in simultaneous pancreas–kidney transplants. *Transplant Proc* 1998;30:253–254.
104. Boudreaux JP, Corry RJ, Dickerman R, Sutherland DE. Combined experience with immediate pancreas retransplantation. *Transplant Proc* 1991;23:1628–1629.
105. Paraskevas S, Gruessner AC, Kandaswamy R, Humar A, Sutherland DER, Gruessner RWG. Pancreas exchange: Single procedure graft pancreatectomy and retransplant for early graft thrombosis. *Acta Chir Austriaca* 2001;33(suppl 74):2.
106. Benedetti E, Coady NT, Asolati M, et al. A prospective randomized clinical trial of perioperative treatment with octreotide in pancreas transplantation. *Am J Surg* 1998;175:14–17.
107. Stratta RJ, Taylor RJ, Lowell JA, et al. Selective use of sandostatin in vascularized pancreas transplantation. *Am J Surg* 1993;166:598–605.

108. Cicalese L, Sileri P, Rastellini C, Mercado P, Asolati M, Benedetti E. Peri-operative octreotide reduces technical complications related to management of exocrine pancreatic secretion after pancreas transplantation. *Acta Chir Austriaca* 2001; 33(suppl 74):19.
109. Fakir M, Cardozo M, St. Louis G, Daloze P, Corman J, Smeesters C. Hyperamylasemia associated with pancreatic graft arterial stenosis in combined kidney-pancreas transplantation. *Transplantation* 1992;53:689-691.
110. Norstein J, Brekke IB, Holdaas H, et al. Arterial stenoses in duct occluded segmental pancreatic grafts treated with percutaneous transluminal angioplasty. *Transplant Proc* 1990;22: 599-601.
111. Sutherland DER, Moudry KC, Goetz FC, et al. Long-term outcome of pancreas transplants functioning at one year. *Transplant Proc* 1989;21:2845-2849.
112. Keener TS, Cyr DR, Mack LA, et al. Sonographic diagnosis of arteriovenous fistula in pancreas transplant. *J Ultrasound Med* 1995;14:149-152.
113. Sakopoulos AMG, Leapman SB, Pescovitz MD. Iliac artery-bladder fistula: A late complication of rejected pancreas transplants with bladder drainage. *Transplant Proc* 1995;27:3008-3009.
114. Tzakis AG, Carroll PB, Gordon RD, et al. Arterial mycotic aneurysm and rupture: A potentially fatal complication of pancreas transplantation in diabetes mellitus. *Arch Surg* 1989;124: 660-661.
115. Fernandez JA, Robles R, Martinez E, et al. Arterioenteric fistula due to cytomegalovirus infection after pancreas transplantation. *Transplantation* 2001;72:966-968.
116. Tan M, DiCarlo A, Stein LA, et al. Pseudoaneurysm of the superior mesenteric artery after pancreas transplantation treated by endovascular stenting. *Transplantation* 2001;72:336-338.
117. Madan AK, Allmon JC, Harding M, et al. Extrapaneatric pseudoaneurysm after pancreas transplantation. *Transplantation* 2001;71:1853-1856.
118. Verni MP, Leone JP, DeRoover A. Pseudoaneurysm of the Y-graft/iliac artery anastomosis following pancreas transplantation: A case report and review of the literature. *Clin Transplant* 2001;15:72-76.
119. Gritsch HA, Shapiro R, Egidi F, et al. Spontaneous arterioenteric fistula after pancreas transplantation. *Transplantation* 1997;63:903-904.
120. Khan TFT, Ciancio G, Burke GW, et al. Pseudoaneurysm of the superior mesenteric artery with an arteriovenous fistula after simultaneous kidney-pancreas transplantation. *Clin Transplant* 1999;13:277-279.
121. Nash PA, Little JS Jr. Arteriovesical fistula after pancreatic transplantation. *J Urol* 1995;154:1861-1862.
122. Lowell JA, Bynon JS, Stratta RJ, et al. Superior mesenteric arteriovenous fistula in vascularized whole organ pancreatic allografts. *Surg Gynecol Obstet* 1993;177:254-258.
123. Phillips BJ, Fabrega AJ. Embolization of a mesenteric arteriovenous fistula following pancreatic allograft: The steal effect. *Transplantation* 2000;70:1529-1531.
124. Angle JF, Matsumoto AH, McGraw JK, et al. Percutaneous embolization of a high-flow pancreatic transplant arteriovenous fistula. *Cardiovasc Intervent Radiol* 1999;22:147-149.
125. Del Pizzo JJ, Jacobs SC, Bartlett ST, et al. Urological complications of bladder-drained pancreatic allografts. *Br J Urol* 1998; 81:543-547.
126. Reed A, Sollinger HW, Knechtle SJ, et al. Ruptured splenic artery aneurysm: An unusual late complication following pancreas transplantation. *Clin Transplant* 1991;5:327-329.
127. West MS, Stevens RB, Metrakos P, et al. Renal pedicle torsion after simultaneous kidney-pancreas transplantation. *J Am Coll Surg* 1998;187:80-87.
128. Roza AM, Johnson CP, Adams M. Acute torsion of the renal transplant after combined kidney-pancreas transplant. *Transplantation* 1999;67:486-488.
129. Kuo PC, Krieger NR, Alfrey EJ, et al. The utility of retroperitoneal kidney placement in simultaneous kidney pancreas transplantation. *Clin Transplant* 1995;9:457-462.
130. Everett JE, Wahoff DC, Statz C, et al. Characterization and impact of wound infection after pancreas transplantation. *Arch Surg* 1994;129:1310-1317.
131. Stratta RJ. Mortality after vascularized pancreas transplantation. *Surgery* 1998;124:823-830.
132. Gruessner RWG, Burke GW, Stratta R, Sollinger H, Benedetti E, Marsh C, Stock P, Boudreaux JP, Martin M, Drangstveit MB, Sutherland DER, Gruessner A. A multicenter analysis of the first experience with FK506 for induction and rescue therapy after pancreas transplantation. *Transplantation* 1996;61:261-273.
133. Smets YFC, van der Pijl JW, van Dissel JT, et al. Infectious disease complications of simultaneous pancreas kidney transplantation. *Nephrol Dial Transplant* 1997;12:764-771.
134. Pirsch JD, Odorico JS, D'Alessandro AM, Knechtle SJ, Becker BN, Sollinger HW. Posttransplant infection in enteric versus bladder-drained simultaneous pancreas-kidney transplant recipients. *Transplantation* 1998;66:1746-1750.
135. Knight RJ, Bodian C, Rodriguez-Laiz G, et al. Risk factors for intra-abdominal infection after pancreas transplantation. *Am J Surg* 2000;179:99-102.
136. Gruessner AC, Barrou B, Jones J, Dunn DL, Moudry-Munns K, Najarian JS, Sutherland DE, Gruessner RW. Donor impact on outcome of bladder-drained pancreas transplants. *Transplant Proc* 1993;25:3114-3115.
137. Malaise J, Squifflet JP, Van Ophem D, Euro SPK Study Group. Does the mode of renal replacement therapy influence the rate of peritoneal infection after simultaneous pancreas kidney (SPK) transplantation? *Transplantation* 2002;74(suppl):566-567.
138. Douzdjian V, Abecassis MM. Deep wound infections in simultaneous pancreas-kidney transplant recipients on peritoneal dialysis. *Nephrol Dial Transplant* 1995;10:533-536.
139. D'Alessandro AM, Sollinger HW, Stratta RJ, Kalayoglu M, et al. Comparison between duodenal button and duodenal segment in pancreas transplantation. *Transplantation* 1989;47:120-122.
140. Gruessner RWG, Sutherland DER, Drangstveit MB, et al. Pancreas transplants from living donors: Short- and long-term outcome. *Transplant Proc* 2001;33:819-820.
141. Papalois BE, Troppmann C, Gruessner AC, et al. Long-term peritoneal dialysis before transplantation and intra-abdominal infection after simultaneous pancreas-kidney transplantations. *Arch Surg* 1996;131:761-766.
142. Douzdjian V, Gugliuzza KK. The impact of midline versus transverse incisions on wound complications and outcome in simultaneous pancreas-kidney transplants: A retrospective analysis. *Transplant Int* 1996;9:62-67.
143. Nakache R, Weinbroum A, Breitman I. Surgical risk of pancreas transplantation: The influence of pretransplant management with peritoneal dialysis. *Transplant Proc* 2001;33:2947.

144. Brayman KL, Stephanian E, Matas AJ, Schmidt W, Payne WD, Sutherland DE, Gores PF, Najarian JS, Dunn DL. Analysis of infectious complications occurring after solid-organ transplantation. *Arch Surg* 1992;127:38–48.
145. Barker RJ, Mayes JT, Schulak JA. Wound abscesses following retroperitoneal pancreas transplantation. *Clin Transplant* 1991;5:403–407.
146. Benedetti E, Troppmann C, Gruessner AC, et al. Pancreas graft loss caused by intra-abdominal infection. *Arch Surg* 1996;131:1054–1060.
147. Rayhill SC, Odorico JS, Heisey DM, Wilson MA, Pirsch JD, D'Alessandro AM, Knechtle SJ, Eckhoff DE, Belzer FO, Sollinger HW. Clinical and laboratory features of pancreatic transplant bladder leaks. *Transplant Proc* 1995;27:3141–3142.
148. Stratta RJ, Gaber AO, Shokouh-Amiri MH, et al. A prospective comparison of systemic-bladder versus portal-enteric drainage in vascularized pancreas transplantation. *Surgery* 2000;127:217–226.
149. Troppmann C, Gruessner AC, Benedetti E, et al. Positive duodenal segment cultures are not associated with increased surgical complications after whole organ, bladder-drained pancreas transplantation in three recipient categories. *Transplant Proc* 1995;27:3101–3103.
150. Barone GW, Sailors DM, Ketel BL. Combined kidney and pancreas transplants through lower transverse abdominal incisions. *Clin Transplant* 1996;10:316–319.
151. Schweitzer EJ, Bartlett ST. Wound complications after pancreatic transplantation through a kidney transplant incision. *Transplant Proc* 1994;26:461.
152. Humar A, Kandaswamy R, Papalois VE, et al. Superficial and deep wound infections developing after kidney transplant. *Transplantation* 2000;69(suppl):S330.
153. Lumbreras C, Fernandez I, Velosa J, Munn S, Sterioff S, Paya CV. Infectious complications following pancreatic transplantation: Incidence, microbiological and clinical characteristics, and outcome. *Clin Infect Dis* 1995;20:514–520.
154. Mosdell DM, Morris DM, Voltura A, et al. Antibiotic treatment for surgical peritonitis. *Ann Surg* 1991;214:543–549.
155. Pfundstein J, Roghmann M-C, Schwalbe RS, et al. A randomized trial of surgical antimicrobial prophylaxis with and without vancomycin in organ transplant patients. *Clin Transplant* 1999;13:245–252.
156. Villacian JS, Paya CV. Prevention of infections in solid organ transplant recipients. *Transplant Infect Dis* 1999;1:50–64.
157. Hakim NS, Gruessner AC, Papalois BE, et al. Duodenal complications in bladder-drained pancreas transplantation. *Surgery* 1997;121:618–624.
158. Nymann T, Shokouh-Amiri MH, Elmer DS, et al. Diagnosis, management, and outcome of late duodenal complications in portal-enteric pancreas transplantation: Case reports. *J Am Coll Surg* 1997;185:560–566.
159. Elkhannas EA, Henry ML, Tesi RJ, Ferguson RM. Late urine leaks after combined kidney–pancreas transplantation. *Transplant Proc* 1994;26:453.
160. Sollinger H, Messing E, Eckhoff D, et al. Urological complications in 210 consecutive simultaneous pancreas–kidney transplants with bladder drainage. *Ann Surg* 1993;218:561–570.
161. Marsh CL, Forg P. The diagnosis and management of urologic complications in nonrenal transplant recipients. *Sem Urol* 1994;12:233–250.
162. Sethi PS, Elkhannas EA, Pollifrone DL, et al. High intravesical pressures and related urologic complications in simultaneous kidney/pancreas transplant recipients. *Transplant Proc* 1995;27:3085–3086.
163. Kaplan SA, Te AE, Blaivas JG. Urodynamic findings in patients with diabetic cystopathy. *J Urol* 1995;153:342–344.
164. Gruessner RWG, Dunn DL, Tzardis PJ, et al. Complications occurring after whole organ duodenopancreatic transplantation: Relation to the allograft duodenal segment. *Transplant Proc* 1990;22:578–579.
165. Esterl RM, Stratta RJ, Taylor RJ, et al. Rejection with duodenal rupture after solitary pancreas transplantation: An unusual cause of severe hematuria. *Clin Transplant* 1995;9:155–159.
166. Bischof TP, Thoeni RF, Melzer JS. Diagnosis of duodenal leaks from kidney–pancreas transplants in patients with duodenovesical anastomoses: Value of CT cystography. *AJR* 1995;165:349–354.
167. Longley DG, Dunn DL, Gruessner R. Detection of pancreatic fluid and urine leakage after pancreas transplantation: Value of CT and cystography. *AJR* 1990;155:997–1000.
168. Eckhoff DE, Ploeg RJ, Wilson MA, D'Alessandro AM, Knechtle SJ, Pirsch JD, Belzer FO, Sollinger HW. Efficiency of ^{99m}Tc voiding cystourethrogram for detection of duodenal leaks after pancreas transplantation. *Transplant Proc* 1994;26:462–463.
169. Tydén G, Tibell A, Groth CG. Pancreatico-duodenal transplantation with enteric exocrine drainage: Technical aspects. *Clin Transplant* 1991;5:36–39.
- 169a. Heredia EN, Ricart MJ, Astudillo E, et al. Pancreas transplantation with enteric drainage: Duodenal segment leak. *Transplant Proc* 2002;34:215.
170. Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis. *Arch Surg* 1993;128:586–590.
171. Büsing M, Hopt UT, Quacken M, et al. Morphological studies of graft pancreatitis following pancreas transplantation. *Br J Surg* 1993;80:1170–1173.
172. Benz S, Bergt S, Obermaier R, et al. Impairment of microcirculation in the early reperfusion period predicts the degree of graft pancreatitis in clinical pancreas transplantation. *Transplantation* 2001;71:759–763.
173. Linder R, Tydén G, Tibell A, et al. Late graft pancreatitis. *Transplantation* 1990;50:257–261.
- 173a. Dreyer DR, Valente JF, Siegel CT, et al. Increased incidence of allograft pancreatitis in patients treated with sirolimus compared to mycophenolate mofetil. *Am J Transplant* 2003;3(suppl 5):523.
174. Esterl RM, Gupta N, Reese JC, et al. Pancreaticocystostomy revision for obstructive pancreatitis and pancreatic fistula after segmental pancreatic transplantation. *Clin Transplant* 1996;10:287–293.
- 174a. Stratta RJ, Sindhi R, Sudan D, et al. Duodenal segment complications in vascularized pancreas transplantation. *J Gastrointest Surg* 1997;1:534–544.
175. Wengrovitz M, Jarowenko MV, Gifford RR, Schtin AG, Mandell MJ, Yang HC. Stone formation as a cause of allograft pancreatitis in the recipient of a combined kidney and pancreas transplant. *Clin Transplant* 1990;4:117–119.
- 175a. Klassen DK, Drachenberg CB, Papadimitriou JC, et al. CMV allograft pancreatitis: Diagnosis, treatment, and histological feature. *Transplantation* 2000;69:1968–1971.

- 175b. Fernandez-Cruz L, Sabater L, Gilabert E, et al. Native and graft pancreatitis following combined pancreas-renal transplantation. *Br J Surg* 1993;80:1429–1432.
176. Bäckman L, Brattström C, Reinholt FP, et al. Development of intrapancreatic abscess—a consequence of CMV pancreatitis? *Transplant Int* 1991;4:116–121.
177. Anand BS, Goodgame R, Graham DY. Pancreatic secretion in man: Effect of fasting, drugs, pancreatic enzymes, and somatostatin. *Am J Gastroenterol* 1994;89:267–270.
178. Burton FR, Garvin PJ, Joshi SN. Human pancreatic graft fistula exocrine suppression by oral pancreatic enzymes. *Transplantation* 1989;47:888–891.
179. Nicholson CP, Barr D, Oeltjen MR, et al. The effect of somatostatin 201–995 on the early course of porcine pancreaticoduodenal allotransplantation. *Transplantation* 1991;51:31–36.
180. Rosenberg L, Dafoe DC, Schwartz R, Campbell DA Jr, Turcotte JG, Tsai ST, Vinik A. Administration of somatostatin analog (SMS 201–995) in the treatment of a fistula occurring after pancreas transplantation. Interference with cyclosporine immunosuppression. *Transplantation* 1987;43:764–766.
181. Cooper MM, Wright FH, Smith JL, Corry RJ. Successful treatment of a high-output fistula with a somatostatin analogue following pancreas transplantation. *Transplant Proc* 1989;21:3738–3741.
182. Wadström J, Gannedahl G, Wahlberg J, et al. Persistent pancreatic fistula after pancreas transplantation treated with fibrin glue and octreotide. *Transplant Proc* 1995;27:3491–3492.
183. Kin S, Tamura K, Nagami H, Nakase A. Effect of preservation on blood flow and production of prostacyclin and thromboxane A₂ in canine segmental pancreatic autografts. *Transplant Proc* 1991;23:1651–1653.
184. Kin S, Stephanian E, Gores P, Shirabe K, Tanaka T, Salazar A, Brayman K, Gruessner R, Sutherland DE. Successful 96-hr storage preservation of canine pancreas with UW solution containing the thromboxane A₂ synthesis inhibitor OKY046. *J Surg Res* 1992;52:577–582.
185. Pi F, Hotter G, Closa D, Rosello-Catafau J, Bulbena O, Badosa F, Morris M, Fernandez-Cruz L, Gelpi E. Effect of a platelet-activating factor antagonist and desferrioxamine administration on eicosanoid production in rat pancreas transplantation. *Transplantation* 1994;57:12–17.
186. Hiraoka K, Kuroda Y, Tanioka Y, Matsumoto S, Kim Y, Sakai T, Fujita H, Hamano M, Suzuki Y, Ku Y, et al. The importance of adenosine and a colloid (dextran 40) in resuscitation of ischemically damaged canine pancreas during preservation by the two-layer method. *Transplantation* 1994;58:1279–1281.
187. Vollmar B, Janata J, Yamauchi JJ, Menger MD. Attenuation of microvascular reperfusion injury in rat pancreas transplantation by L-arginine. *Transplantation* 1999;67:950–955.
188. Mayer H, Schmidt F, Thies F, Ryschich E, Gebbard MM, Herfarth C, Klar E. Characterization and reduction of ischemia/reperfusion injury after experimental pancreas transplantation. *J Gastrointest Surg* 1999;3:162–166.
189. Benz S, Schnabel R, Weber H, Pfeffer F, Wiesner R, Von Breitenbuch P, Nizze H, Schareck W, Hopt UT. The nitric oxide donor sodium nitroprusside is protective in ischemia/reperfusion injury of the pancreas. *Transplantation* 1998;66:994–999.
190. Esterl RM Jr, Stratta RJ, Taylor RJ, Sindhi R, Castaldo P, Sudan D, Lowell JA. Diagnosis and treatment of symptomatic peripancreatic fluid collections after pancreas transplant. *Transplant Proc* 1995;27:3057–3058.
191. Patel BK, Garvin PJ, Aridge DL, Chenoweth JL, Markivee CR. Fluid collections developing after pancreatic transplantation: Radiologic evaluation and intervention. *Radiology* 1991;181:215–220.
192. Zapas JL, Light JA, Buck DR, et al. Infected transplant pancreatic pseudocyst managed by catheter drainage and pancreatico-ileostomy. *Nephrol Dial Transplant* 1997;12:827–830.
193. Shlansky-Goldberg R, Cope C, McGuckin J, et al. Percutaneous management of a bladder-drained pancreas transplant pseudocyst by a trans cystic approach. *Transplantation* 1997;64:1568–1571.
194. Dubernard JM, Traeger J, Piatti PM, Gelet A, Yafi SEL, Martin X, Devonec M, Henriot M, Kamel G, Canton F, Codas H, Touraine JL. Report of 54 human segmental pancreatic allografts prepared by duct obstruction with neoprene. *Transplant Proc* 1985;27:312–314.
195. Kubota K, Reinholt FP, Tyden G, Groth CG. Pancreatic juice cytology for monitoring pancreatic grafts in the early postoperative period. *Transplant Int* 1992;5:133–138.
196. Burton FR, Burton MS, Garvin PJ, Joshi SN. Enteral pancreatic enzyme feedback inhibition of the exocrine secretion of the human transplanted pancreas. *Transplantation* 1992;54:988–992.
197. Montorsi M, Zago M, Mosca F, Capussotti L, Zotti E, Ribotta G, Fegiz G, Fissi S, Roviato G, Peracchia A, et al. Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: A prospective, controlled, randomized clinical trial. *Surgery* 1995;117:26–31.
198. Secchi A, Di Carlo V, Martinenghi S, La Rocca E, Caldara R, Staudacher C, Ferrari G, Castoldi R, Torri G, Pozza G. Octreotide administration in the treatment of pancreatic fistulae after pancreas transplantation. *Transplant Int* 1992;5:201–204.
199. Zanolli ML, Guerra EE, Costa LF, Vitola SP, Garcia VD, Cantisani GP. Duct-enterostomy as a treatment of pancreatic fistula in a bladder-drained pancreas transplant. *Transplant Proc* 1992;24:815–816.
200. Prasad GVR, Abidi SM, McCauley J, et al. Vitamin K deficiency with hemorrhage after kidney and combined kidney-pancreas transplantation. *Am J Kidney Dis* 1999;33:963–965.
- 200a. Barone GW, Webb JW, Hudec W. The enteric drained pancreas transplant: Another potential source of gastrointestinal bleeding. *Am J Gastroenterol* 1998;93:1369–1371.
201. Troppmann C, Papalois BE, Chiou A, et al. Incidence, complications, treatment, and outcome of ulcers of the upper gastrointestinal tract after renal transplantation during the cyclosporine era. *J Am Coll Surg* 1995;180:433–443.
202. Bingener-Casey J, Esterl RM Jr, Washburn KW, Cigarroa FG, Abrahamian GA, Halff GA. Tc-99-labeled red blood cell scanning localizes anastomotic hemorrhage between the distal ileum and duodenal stump of an enteric-drained pancreas transplant. *Clin Nucl Med* 2002;27:205–206.
203. Hickey DP, Bakthavatsalam R, Bannon CA, et al. Urological complications of pancreatic transplantation. *J Urol* 1997;157:2042–2048.
204. Sollinger HW, Odorico JS, Knechtle SJ, et al. Experience with 500 simultaneous pancreas-kidney transplants. *Ann Surg* 1998;228:284–296.
205. Gettman MT, Levy JB, Engen DE, et al. Urological complications after kidney-pancreas transplantation. *J Urol* 1998;159:38–43.

206. Cranston D, Little D. Urological complications after renal transplantation. *Kidney Transplant* 2001;29:435–444.
207. Stratta RJ, Taylor RJ. Prevention and management of hematuria in combined pancreas–kidney transplant recipients with pancreaticoduodenocystostomy. *Transplant Proc* 1992;24:788–790.
208. Douzjian V, Gugliuzza KK, Fish JC. Urologic complications after simultaneous pancreas–kidney transplantation: Hand-sewn versus stapled duodenocystostomy. *Clin Transplant* 1995;9:396–400.
209. Paduch DA, Conlin M, Dematos A, et al. Arterial duodenovesical fistula after simultaneous pancreas and kidney transplantation. *J Urol* 2000;164:1296.
210. Rhee BK, Bretan PN Jr, Stoller ML. Urolithiasis in renal and combined pancreas/renal transplant recipients. *J Urol* 1999;161:1458–1462.
211. Hahnfeld LE, Nakada SY, Sollinger HW, et al. Endourologic therapy of bladder calculi in simultaneous kidney–pancreas transplant recipients. *Urology* 1998;51:404–407.
212. Ciancio G, Burke GW, Nery JR, et al. Urethritis/dysuria after simultaneous pancreas–kidney transplantation. *Clin Transplant* 1996;10:67–70.
213. Elkhammas EA, York HJP, Ferguson T, et al. Pancreas transplantation and dysuria. *J Urol* 1994;152:881–883.
214. Tom WW, Munda R, First R. Autodigestion of the glans penis and urethra by activated transplant pancreatic exocrine enzymes. *Surgery* 1987;102:99–101.
215. Davies D, Horton PJ, Gow E, et al. Ulceration of the urethral meatus after simultaneous pancreas–kidney transplantation. *Australas J Dermatol* 2000;41:95–97.
216. See WA, Smith JL. Urinary levels of activated trypsin in whole-organ pancreas transplant patients with duodenocystostomies. *Transplantation* 1991;52:630–633.
217. See WA, Smith JL. Urinary trypsin levels observed in pancreas transplant patients with duodenocystostomies promote in vitro fibrinolysis and in vivo bacterial adherence to urothelial surfaces. *Urol Res* 1992;20:409–413.
218. Van der Pijl JW, Smets YFC, de la Fuente R, et al. Urologic infections and problems after 50 simultaneous pancreas–kidney transplantations. *Transplant Proc* 1995;27:3105.
219. De la Fuente RB, Van der Pijl JW, Ringers J, et al. Ballooning of the duodenal segment after a pancreas–kidney transplantation. *J Urol* 1996;155:1384.
220. Torigian DA, Banner MP, Ramchandani P. Imaging urologic complications of pancreas transplantation with bladder drainage. *J Clin Imag* 2000;24:132–138.
221. Taylor RJ, Mays SD, Grothe TJ, Stratta RJ. Correlation of preoperative complications following pancreas transplantation. *J Urol* 1993;150:1185–1188.
222. Lin DW, Kuhr CS, Marsh CL. Endoscopic treatment of bladder outlet obstruction in men after pancreas transplantation. *J Urol* 1999;162:335–338.
223. Ciancio G, Burke G, Lynne C, et al. Urodynamic findings following bladder-drained simultaneous pancreas–kidney transplantation. *Transplant Proc* 1997;29:2912–2913.
- 223a. Ciancio G, Burke GW, Roth D, et al. Reflux pancreatitis after simultaneous pancreas–kidney transplantation by alpha 1 blocker. *Transplantation* 1995;60:760–761.
- 223b. Ciancio G, Montalvo B, Roth D, et al. Allograft pancreatic duct dilatation following bladder drained simultaneous pancreas–kidney transplantation: Clinical significance. *JOP* 2000;1:4–12.
224. Nghiem DD, Kessler GM, Olson PR. Effects of long-term exposure to urine on proliferative lesions of the duodenum in bladder-drained pancreas transplants. *Transplant Proc* 1995;27:3004–3006.
225. Cuellar DC, Sklar GN. Penile prosthesis in the organ transplant recipient. *Urology* 2001;57:138–141.
226. Ciancio G, Burke GW, Nery J, et al. Successful management of calyceal fistula following simultaneous pancreas–kidney transplantation. *Am Surg* 1998;64:267–269.
227. Melvin WS, Bumgardner GL, Davies EA, et al. The laparoscopic management of post-transplant lymphocele. *Surg Endosc* 1997;11:245–248.
228. Stratta RJ, Weide LG, Sindhi R, et al. Solitary pancreas transplantation: Experience with 62 consecutive cases. *Diabetes Care* 1997;20:362–368.
229. Humar A, Kandaswamy R, Drangstveit MB, et al. Surgical risks and outcome of pancreas retransplants. *Surgery* 2000;127:634–640.
- 229a. Bloom DR, Olivares M, Rehman L, et al. Long-term pancreas allograft outcome in simultaneous pancreas–kidney transplantation: A comparison of enteric and bladder drainage. *Transplantation* 1997;64:1689–1695.
230. Zibari GB, Boykin KN, Sawaya DE, et al. Pancreatic transplantation and subsequent graft surveillance by pancreatic portal-enteric anastomosis and temporary venting jejunostomy. *Ann Surg* 2001;233:639–644.
231. Gruessner AC, Sutherland DER. Pancreas transplant outcomes for United States (US) cases reported to the United Network for Organ Sharing (UNOS) and non-US cases reported to the International Pancreas Transplant Registry (IPTR) as of October 2000. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants 2000*. Los Angeles: UCLA Tissue Typing Laboratory; 2001:45–72.
232. Gruessner RW, Kendall DM, Drangstveit MB, Gruessner AC, Sutherland DE. Simultaneous pancreas–kidney transplantation from live donors. *Ann Surg* 1997;226:471–482.
233. Gruessner AC, Sutherland DER. Pancreas transplants for United States (US) and non-US cases as reported to the International Pancreas Transplant Registry (IPTR) and to the United Network for Organ Sharing (UNOS). In: Cecka JM, Terasaki PI, eds. *Clinical Transplants 1997*. Los Angeles: UCLA Tissue Typing Laboratory; 1998:45–59.
234. Gruessner AC, Sutherland DER. Analysis of United States (US) and non-US pancreas transplants as reported to the International Pancreas Transplant Registry (IPTR) and to the United Network for Organ Sharing (UNOS). In: Cecka JM, Terasaki PI, eds. *Clinical Transplants 1998*. Los Angeles: UCLA Tissue Typing Laboratory, 1999:53–71.

9.2.3

Posttransplant Infections

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Over the past 20 years pancreas transplantation has emerged as an important, highly effective therapy in the treatment of patients who suffer diabetes mellitus. International Pancreas Transplant Registry (IPTR) data indicate that over 1,000 pancreatic allografts have been transplanted yearly since 1995, with steady improvements in graft and patient survival¹ (chapter 20). Refinements in surgical technique, the development and use of immunosuppressive drugs, in particular recently available agents in balanced combinations, and prophylactic measures to prevent infection have spurred the growth of this field. However, even today the solid organ transplant recipient remains at increased risk of developing any number of serious infectious complications. Up to 80% of solid-organ transplant recipients will suffer an infectious complication during the first year posttransplant and infection remains a major cause of morbidity and mortality in this patient population.² Of note, among pancreas transplant recipients it has been estimated that the average patient will experience two to three episodes of infection per annum.³ Although many types of infections are similar to those experienced by all groups of immunosuppressed solid-organ transplant recipients, several are unique to individuals who undergo pancreas transplantation.

The range of potential pathogens that may cause disease in the immunosuppressed host is prodigious. Not only are common endogenous and nosocomial flora involved, but so-called “opportunistic” or “atypical” pathogens that rarely cause disease in normal individuals also affect this patient population. To understand the epidemiology of infectious complications that effect pancreas transplant recipients it is helpful to consider several factors: time frame of infection relative to transplantation, type and degree of immunosuppression as well as the need for antirejection therapy, and the method of exocrine drainage of the graft, the latter being closely linked to the occurrence of specific types of surgical infectious complications.

Not surprisingly, the period of greatest risk of infection corresponds with that of most intense immunosuppression—characteristically during the first year posttransplant and immediately after any period of immunosuppressive induction or antirejection therapy, in particular after repeated episodes of rejection treated in close temporal association. The period between 1 and 6 months posttransplant is typically the time of maximal immunosuppression, and this leads to a significantly heightened infection risk. Infectious complications in the first month posttransplant are typically caused by endogenous or nosocomial flora, which are capable of causing disease in an immunocompetent host. These include surgical site infections (SSIs) including intra-abdominal infections, postoperative or ventilator-associated pneumonia, urinary tract infections (UTIs) associated with prolonged in-dwelling urinary catheters, and bacteremic episodes that often are associated with central venous catheter infections.^{4,5} The causative pathogens are invariably both gram-positive and -negative bacteria as well fungi such as *Candida* spp., often in combination. Subsequently, infections due to more aggressive fungal microbes such as *Aspergillus* spp. and viral pathogens predominate, the latter of which may become active after being dormant in the host or by being transferred from the donor by the allograft.^{6,7} It is highly likely that the duration of immunosuppression as well the intensity are key factors leading to the occurrence of these infections.

It is of critical importance for the clinician to be aware of the epidemiology of infection in this patient population during this initial window of vulnerability, as characteristic patterns of maximal frequency of opportunistic viral and fungal pathogens have been identified. These patterns of infections may be simplified by considering an early cluster of viral agents that occurs with peak frequency between 2 to 3 months posttransplant and a late cluster that more commonly occurs

between 4 to 9 months posttransplant. The early group includes cytomegalovirus (CMV), adenoviruses, hepatitis B and C, and human herpes virus (HHV)-6.⁶⁻¹² The later cluster includes varicella-zoster and polyoma viruses.¹³ Epstein-Barr virus (EBV) may cause disease throughout the first year posttransplant.¹⁴ The opportunistic fungi can similarly be observed to cluster with *Candida* and *Aspergillus* species, causing infections in the first 2 to 3 months posttransplant^{15,16} whereas *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Pneumocystis carinii* most often occur later during the first year.^{17,18}

After the first 6 to 12 months the majority of transplant recipients will exhibit similar patterns of infectious disease morbidity as the general population, with frequent respiratory infections secondary to pneumococcal infections, viral influenza, and uncomplicated UTIs. However, opportunistic infections can occur at any time, and increased immunosuppression secondary to treatment of acute rejection may increase the susceptibility to and alter the temporal pattern of these less common infectious agents. A high index of suspicion for the presence of infection must be maintained at all times when assessing the immunosuppressed patient, as the typical localizing signs of infection and inflammation may be blunted or even absent due to the anti-inflammatory action of the immunosuppressive regimen.

An important component of the transplant process is the preoperative assessment of both the recipient and donor for infectious disease that may cause complications in the newly immunosuppressed recipient. With respect to the donor, active infection invariably precludes use of the organ and therefore an important evaluation is the determination of the CMV and EBV serological status because these agents are readily transmitted to the seronegative recipient. The prevalence of both of these agents is on the order of 90% in the adult population. Consequently, the CMV seronegative recipient is at high risk of developing a primary infection following transplantation, in particular if the donor is CMV seropositive. Whether multiagent prophylactic antiviral therapy will reduce the burden of disease in the seronegative graft recipient is currently the subject of study, but a number of centers are increasing the duration of intravenous (IV) antiviral prophylaxis for this group of patients. Cultures of organ preservation fluid are routinely performed, but appropriate antibiotic therapy can ordinarily prevent positive cultures from resulting in clinically significant disease.¹⁹ A thorough pretransplant history and physical examination of the recipient is essential to minimize the risk of infectious complication secondary to a latent or indolent infectious process. Routine viral studies are obtained, vaccinations are brought up to date, and appropriate perioperative prophylaxis is employed.

Bacterial Infections

Bacterial infections are common in the first 30 days posttransplant, often being related to the surgical intervention itself. The risk of nosocomial bacterial infection is related to

the site of surgery as well as to the site of and continued presence of any catheters, lines, drains, endotracheal tube, or other breaks in the skin. The most common sites of infection are the urinary tract, surgical site, lungs, and the blood stream. The risk of nosocomial bacterial infection is directly related to host factors including underlying diseases such as diabetes or cirrhosis, obesity, and chronic pulmonary disease, as well as to technical and management factors including the preoperative preparation, length and technique of operation, presence of a hematoma or seroma, and need for prolonged urinary catheterization, prolonged mechanical ventilation, or prolonged central venous catheterization. Surgical complications such as anastomotic leaks are invariably associated with serious bacterial infections as well.

The urinary tract is a common site of bacterial infection, in particular in the bladder-drained pancreas transplant recipient. Bacteriuria may be detected in up to 83% of renal transplant patients²⁰ with an attendant increased risk of systemic sepsis and wound infection. The rate of bacteriuria in the bladder-drained pancreas transplant population is not established, but is thought to be similar, and one group of investigators has documented that ~30% to 40% of such patients develop UTIs during the first 3 years posttransplant.²¹ The most common pathogens isolated are gram-negative aerobes, enterococci, and *Candida* spp. The risk factors associated with increased incidence of UTIs include prolonged catheterization, hemodialysis, and antibiotic prophylaxis in excess of 48 hours.²² The use of ureteral stents is associated with an increased rate of UTIs.²³ The use of prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) is common in transplant patients, primarily to decrease the risk of several opportunistic pathogens including *P. carinii*, *Toxoplasma gondii*, *Listeria monocytogenes*, and *Legionella pneumonia*; however, this practice likely also reduces the risk of UTIs caused by more typical pathogens in renal and bladder-drained pancreas transplant patients receiving this therapy.²⁴ Diagnosis of UTI in the transplant patient is based on clinical suspicion and urinalysis and culture. The typical findings of dysuria, hesitance, and frequency are often absent, with the only clinical manifestations of the UTI potentially being fever or an elevated white blood cell count. Treatment is often empirical and broad spectrum, in particular during the first months posttransplant. An increased risk of bacterial or fungal UTI is not ordinarily seen in recipients of other solid-organ allografts who do not require a long duration of urinary catheterization.

Infection of the surgical site is potentially a source of major morbidity and occasional graft loss and mortality in the solid organ transplant patient. Surgical site or wound infections are classified according to the structures involved. Infections above the fascia are superficial, infections below the fascia are deep, and combined infections involve elements of both the superficial and deep compartments of the wound.^{25,26} Perioperative antibiotics are given to decrease the risk of surgical site infection and in general include a broad-spectrum antibacterial agent and fluconazole. Antibiotics are typically

continued for 24 to 72 hours posttransplant although data to support this practice and the specific selection of agents are lacking. In many series, pancreas allografts recipients exhibit a high rate of wound infection with a 10% to 40% superficial, 15% to 22% deep, and 8% combined infection rate.^{27,28} At one center, low rates of such infections have been reported (2.4%) with the exception of patients who undergo conversion from bladder to enteric exocrine draining in whom the wound infection rate was 1%.²⁹ These wound infections carry a great potential morbidity and a substantial mortality and require an aggressive approach to diagnosis and therapy. In addition, retransplantation of such patients is associated with a high rate of recurrent infection often due to the same pathogens,³⁰ and the use of pancreata from obese donors has been associated with infection as well.³¹

Pathogenic microbes are predictable based on the type of operation undertaken. Wound infections in renal and bladder-drained pancreas transplantation are caused by the endogenous flora of the skin and bladder: gram-positive and -negative aerobes, respectively, with occasional *Candida* and enterococci. However, pancreas transplant wound infections are often polymicrobial with frequent gram-positive, fungal, and resistant gram-negative pathogens present. These infections require broad-spectrum antimicrobial therapy with a carbapenem or extended-spectrum penicillin along with vancomycin or linezolid, and often amphotericin B if fungi are identified.

The diagnosis of wound infection is often subtle and findings may be limited to fever, elevated white blood count, or wound drainage with a deceptively innocuous appearance. Any wound drainage should be examined by gram stain and culture, and suspicion or evidence of infection should result in opening of the wound. In addition, imaging should be undertaken to rule out an infection in the deep surgical space with prompt exploration and/or drainage should that result be obtained. Delays in diagnosis or appropriate therapy can lead to substantial morbidity and mortality in this patient population. Prolonged, broad-spectrum antimicrobial therapy is employed and immunosuppression is minimized in potentially life-threatening abdominal infections. Early consideration of re-exploration, potentially with graft pancreatectomy, should occur.

The development of postoperative pneumonia varies with the type of transplantation and is associated with a marked mortality of 20% to 60%.^{32,33} Renal transplantation is associated with the lowest incidence (1% to 2%) and lung transplantation with the highest (22%). The rate of postoperative pneumonia after pancreas transplantation is not clearly defined but is thought to be approximately 5%. The most common pathogens identified are the gram-negative aerobes, staphylococci, and *Legionella* spp. Frequently, *Candida* or CMV may be obtained along with bacterial pathogens, in particular in the first 2 to 3 months posttransplant. These findings are clinically significant, and active CMV pneumonitis is a significant risk factor for the development of concurrent

bacterial pneumonia. Several risk factors may be at play that may predispose the patient to the development of pneumonia. These may include prolonged mechanical ventilation, thoracic surgery, pulmonary edema, and intense immunosuppression or treatment of acute rejection. Pleural effusions should be aggressively drained and cultured because the progression of an infected effusion to empyema in a transplant patient is associated with high mortality.

Bacteremia in the transplant population, as in the general hospital population, may occur secondary to seeding along a vascular access device or as a result of hematogenous spread from another source. Urinary tract infection, SSI, and pneumonia are risk factors for the development of bacteremia, as is prolonged vascular catheterization. Additional risk factors include receiving a cadaveric allograft, leukopenia, and anti-rejection therapy. Bacteremia in the immunosuppressed patient may present as fever, leukocytosis, or leukopenia. Consequently, obtaining blood cultures among patients who develop these symptoms and signs is mandatory. Suspicion of bacteremia should prompt removal and culture of intravascular devices and a source for other primary sources of sepsis. Because the mortality associated with bacteremia and septic shock in transplant patients exceeds 50%, broad-spectrum antimicrobial therapy, an aggressive approach to source control, and the minimization of immunosuppression all are indicated in these patients.

Several atypical bacterial infections are seen in the solid organ transplant population. These include mycobacteria such as *Mycobacterium tuberculosis*, *Nocardia* spp., and *L. monocytogenes*, all of which are associated with high rates of morbidity and mortality. Mycobacterial infections are 50 to 100 times more frequent in the transplant population than they are in the general population and can be fatal in 30% of cases. Most occur within the first 6 to 12 months after transplantation and are associated with intense immunosuppression and antirejection therapy.³⁴ Infection typically is related to reactivation of latent disease or transmission with the transplanted graft. Unfortunately, establishing the diagnosis is complicated by the lack of a reaction to skin testing due to exogenous immunosuppression. Consequently, clinical suspicion must be high, and bronchoscopic evaluation with biopsy, acid-fast stain, and culture should be employed when mycobacterial infection is suspected. Treatment is multidrug therapy with isoniazid, ethambutol, rifampin, and other agents. Isoniazid prophylaxis should be considered in high-risk patient populations and individuals with a history of significant exposure or incompletely treated disease.

Listeria monocytogenes may be associated with pneumonia, bacteremia, or, most ominously, with meningitis in the transplant population. *Listeria* has been associated with a 26% mortality in renal transplant patients; consequently, a thorough evaluation of any immunosuppressed patient must be undertaken when there is clinical suspicion of meningitis, and empirical therapy for meningitis should include appropriate coverage of this pathogen (e.g., ampicillin plus an aminogly-

coside).³⁵ The extended-spectrum penicillins will also provide adequate coverage.

Nocardia infection most commonly presents with pulmonary symptoms and signs but disseminated disease may involve the skin, eye, and brain. The clinical picture is often nonspecific in that patients may develop fever, chills, malaise, occasional cough, dyspnea, headache, or mental status changes either alone or in combination. These infections carry a mortality of 25% to 50% and must be aggressively diagnosed and treated.³⁶ The diagnosis is made by microscopic examination of sputum or lung (or on occasion brain) biopsy tissue aided by Kinyoun and Ziehl-Neelsen staining. Treatment is with high-dose TMP-SMX and an aminoglycoside (such as amikacin) with continued treatment with oral TMP-SMX, preferably for life.

Fungal Infections

Historically, solid-organ transplantation has been associated with a significant risk of fungal infection. However, the incidence of fungi as pathogens has increased in the era of broad-spectrum antibacterial prophylaxis and empirical therapy, and an increased incidence of resistant fungal infections also has been observed. Fungal infections are most common following liver and pancreas transplantation, where the incidence approaches 40%.³⁷ These infections are less common following renal transplantation, where only 5% of transplants will be complicated by a fungal infection. Invasive fungal infections are associated with a mortality of 30% to 50% in this patient population. As noted previously, the majority of fungal infections occur during the first 3 to 4 months after transplant during the period of intense immunosuppression. Sources of fungal pathogens include endogenous pathogens in the oral cavity and gastrointestinal (GI) tract or soil organisms in the environment.

The most common fungal pathogens are various species of *Candida*.³⁸ Candidal overgrowth of the oral and GI tract is common and prophylaxis is often employed consisting of topical nystatin or clotrimazole. Risk factors associated with invasive candidal disease include diabetes, neutropenia, intense immunosuppression, and prolonged administration of antibacterial antibiotics. Despite prophylaxis, severe oropharyngeal or esophageal candidal infection can occur, the latter requiring fluconazole or amphotericin B therapy for 10 to 14 days. Candidemia is most often associated with the presence of chronic in-dwelling catheters, and its identification in the bloodstream mandates catheter removal and treatment with an antifungal agent for 14 to 21 days. Tissue-invasive candidiasis also can occur, although most often it is in the setting of a perforation of the GI tract, an anastomotic breakdown, a deep surgical site infection, or a concomitant GI infection such as CMV gastroenteritis or colitis.

Widespread use of triazole agents such as fluconazole has led to more frequent isolation of resistant *Candida* species

such as *C. glabrata*, *kruseii*, and *parapsilosis*. Most invasive *Candida* infections should be treated with amphotericin B, although a new antifungal agent, caspofungin, shows great promise in the treatment of *Candida* and invasive aspergillosis (see below). Caspofungin is an echinocandin that acts to block the synthesis of 1,3 β -D-glucan, an essential element of the fungal cell wall. It is well tolerated with a side effect profile that compares favorably to amphotericin B. Importantly, caspofungin and amphotericin B appear to act in an additive manner, and cross-resistance has not been identified. Clinical trials comparing caspofungin and amphotericin in patients with human immunodeficiency virus and oral or esophageal candidiasis show equivalence with trends toward superior outcomes among patients receiving caspofungin.^{39,40} It is highly likely that this will be an important drug in treating invasive fungal infections in solid-organ transplant patients.

Aspergillosis will occur in 1% to 4% of transplant patients, most commonly in liver and lung transplants. Half of these patients will go on to develop disseminated disease and these individuals exhibit a mortality rate in excess of 80%.⁴¹ Most patients with aspergillosis present in a similar fashion to patients with atypical bacterial pneumonia. The high-risk setting of lung or liver transplantation or the failure to respond to appropriate antibiotic therapy in a lower risk patient should prompt an invasive diagnostic approach. The diagnosis is established by staining and microscopic visualization after tissue biopsy, and amphotericin B therapy should be initiated. Invariably, patients will require 1.5 to 2 g of drug therapy, and surgical intervention may be required in refractory cases or among patient who exhibit recrudescence. Patients who exhibit renal dysfunction either before or during therapy are candidates for liposomal amphotericin B treatment, although it is extremely expensive. Itraconazole also is employed,⁴² and increasingly caspofungin is used in refractory cases. Dissemination to the central nervous system (CNS) may result in brain abscesses that are nearly uniformly fatal, although survivors are reported after antifungal therapy and neurosurgical resection.⁴³

Other fungi seen as pathogens in solid organ transplant patients include *C. neoformans*, *C. immitis*, *Blastomyces dermatitidis*, *H. capsulatum*, and the *Mucor* and *Rhizopus* spp. Infections with these fungi occur in specific settings and present as specific syndromes that should be considered by the clinician caring for the immunosuppressed patient.

Cryptococcus neoformans is the second leading cause of invasive fungal infection in solid organ transplant patients. This pathogen may cause pneumonia or meningitis, and patients with pulmonary disease often have CNS involvement as well. Skin nodules are on occasion seen. Diagnosis is by India ink staining and by testing for cryptococcal antigen in cerebrospinal fluid or sputum. Treatment with amphotericin B followed by oral fluconazole should be implemented.⁴⁴

Coccidioides immitis is endemic in the Southwestern United States and Mexico. Between 7% to 9% of solid organ transplant patients residing in this area will develop coccid-

omycosis with an associated mortality of 25% in pulmonary cases and up to 70% in disseminated cases.⁴⁵ The presentation of disease is variable as multiple organ systems may be involved. The diagnosis must be made by microscopy, antigen detection, or culture of tissue. The treatment is prolonged amphotericin B therapy.

Histoplasmosis and blastomycosis are endemic to the American Midwest in the Mississippi and Ohio River valleys. Invasive disease, either reactivation of latent fungi or new infection, occurs in up to 2% of solid-organ transplant recipients, with the highest incidence in the endemic area. Invasive disease spreads from the lungs to the skin and bone marrow. Biopsy and culture may be obtained from skin lesions if present or from bone marrow. Amphotericin B or itraconazole are used as therapy.⁴⁶

Mucor and *Rhizopus* spp. are soil fungi that, when inhaled, may cause a highly morbid invasive rhinocerebral or disseminated infection in the profoundly immunosuppressed patient and in diabetics with poor glycemic control. The diagnosis is established by biopsy, and treatment is surgical debridement with adjuvant antifungal therapy with amphotericin B with the occasional addition of 5-flucytosine, itraconazole, or rifampin.⁴⁷

Viral Infections

Viral infections are increasingly recognized as an important cause of morbidity and mortality in solid-organ transplant patients. Viruses that are endemic and of little clinical concern in the wider population may produce an overwhelming infection in the host with suppressed cellular immunity. The recent appreciation of the immunomodulatory effect of several opportunistic viral pathogens provides even more reason for continued development of effective prophylaxis, diagnosis, and treatment modalities for this class of infective agent. Immunosuppressed transplant recipients may develop clinically important viral infections by reactivation of latent virus, transmission of virus via the donor graft or via blood transfusion, or exposure to virus in the environment.

The human herpes viruses are important pathogens in the solid-organ transplant population (Table 9.2.3.1). These viruses commonly cause disease during periods of the maximal immunosuppression, in particular early after transplant and after antirejection therapy. These agents include many of the most important viral pathogens facing the immunosuppressed patient including CMV, EBV, the herpes simplex viruses (HSV-1 and HSV-2), and the varicella-zoster virus (VZV).

Cytomegalovirus infection affects 30% to 75% of patients following solid-organ transplant, primarily occurring within 2 weeks to 3 months posttransplant. The highest risk for CMV infection occurs in seronegative recipients receiving a graft from a CMV-seropositive donor (the D+/R- graft).⁴⁸ Lung and heart-lung transplant recipients have the highest rate

TABLE 9.2.3.1. Human herpes viruses.

Virus	Eponym	Clinical syndromes
HHV-1	Herpes simplex virus-1	Mucocutaneous disease, primarily oral-labial ocular keratitis, HSV encephalitis
HHV-2	Herpes simplex virus-2	Mucocutaneous disease, primarily genital ocular keratitis
HHV-3	VZV	Chickenpox, "shingles," pneumonitis, encephalitis
HHV-4	EBV	Infectious mononucleosis, hepatitis, pneumonitis, PTLD, Burkitt's lymphoma
HHV-5	CMV	Mononucleosis, pneumonitis, hepatitis, gastroenteritis, retinitis
HHV-6	Roseola (6B)	Childhood febrile exanthema, mononucleosis, encephalitis, pneumonitis, disseminated disease
HHV-7		No clear clinical entities
HHV-8	Kaposi agent	Cutaneous lymphomas

of CMV disease at 50% to 80% incidence. Pancreas and kidney-pancreas transplant patients have a 50% incidence, and isolated kidney, heart, or liver transplant recipients face an 8% to 35% risk of developing active CMV disease.⁴⁹ The most severe disease is primary infection, as seen in the D+/R- population. Superinfection is typically intermediate in severity, and reactivation of latent disease is most often comparatively mild.⁵⁰ The range of clinical disease is vast, ranging from asymptomatic infection—detectable only by change in anti-CMV titer or isolation of virus in blood, urine, or sputum—to invasive disease that may affect lung, liver, pancreas, intestine, or retinas. A typical mild infection will produce a mononucleosis-like syndrome including fever, malaise, and myalgias, often accompanied by leukopenia. More severe disease will clinically manifest differing signs and symptoms depending on the site(s) of invasive infection. Gastrointestinal ulceration with occasional hemorrhage is seen in GI disease, CMV pneumonitis may produce respiratory insufficiency and failure, CMV hepatitis may lead to liver failure, and CMV retinitis may produce vision changes leading to blindness.

Previously, the diagnosis was established by observing an increase in anti-CMV titer by fourfold or by direct observation of CMV inclusion bodies in biopsy specimens. More recently these techniques have been supplanted by the rapid "shell-vial" culture, in which virus is grown in culture with fibroblasts and examined by immunofluorescence microscopy after incubation with anti-CMV immunofluorescence-linked monoclonal antibody.⁵¹ A rapid antigenemia assay is also available that measures the levels of the pp65 CMV antigen in sample fluid, but accurate results depend on the presence of a normal white blood cell count.⁵² More recently the polymerase chain reaction (PCR) has been used to measure viral copy number in peripheral leukocytes, and, like the antigenemia assay, may permit early diagnosis of subclinical CMV infection in at-risk patients.⁵³ Authors differ in preference be-

tween these two modalities, but it is clearly useful to have both techniques in the diagnostic armamentarium.

Given the high prevalence and significant morbidity of CMV disease, prophylaxis with IV followed by oral ganciclovir for several months posttransplant is commonly practiced. Additional prophylaxis is routinely given with initiation of antirejection therapy. Several randomized clinical trials have shown ganciclovir prophylaxis to be superior to prophylaxis with acyclovir in preventing both reactivation and primary CMV disease in solid organ transplant patients, including pancreas and kidney-pancreas transplant recipients.⁵⁴⁻⁵⁷ A second approach to this problem, so-called "pre-emptive therapy," is the assiduous monitoring of at-risk patients with protocol antigenemia or PCR assays followed by empirical therapy with ganciclovir should levels rise above a predetermined threshold. This approach, while somewhat cumbersome, has also led to reductions in the burden of CMV disease in liver transplant patients,^{58,59} and some combination of prophylaxis and surveillance with empirical therapy is currently practiced in most transplant centers. Close monitoring with pre-emptive therapy has not been shown to be superior to treatment based on symptomatic disease in renal transplant patients⁶⁰ and consequently the main focus in this population is on prophylaxis. Ganciclovir prophylaxis is used for lung, heart-lung, and heart transplantation as well,^{61,62} but there are little data to guide the practice of surveillance and pre-emptive therapy in these patient groups. Similarly, there are limited data to guide therapy in pancreas transplantation, and practice in this patient population is based on studies in groups of recipients of other allografts.

Tissue-invasive CMV infection should be treated with IV ganciclovir for 2 weeks, following which either oral ganciclovir or oral valganciclovir should be continued for 4 weeks to prevent recurrence. Anti-CMV immune globulin is available and is commonly added to ganciclovir for the treatment of serious life-threatening invasive CMV infection, although studies of this agent are limited to its use in prophylaxis and are equivocal in showing efficacy.^{63,64} Foscarnet (trisodium phosphonoformate) is used in those rare instances where ganciclovir-resistant strains of CMV are isolated as this drug provides similar efficacy to ganciclovir but is associated with a higher toxicity profile.⁶⁵

The herpes simplex viruses commonly cause mucocutaneous disease of the oropharynx and buccal mucosa (HSV-1) and the genitalia (HSV-2). In profoundly immunosuppressed patients these agents may cause disseminated disease, including hepatitis, encephalitis, and pneumonitis. Most of these infections are felt to be reactivation of latent virus,⁶⁶ and the highest risk is in lung and heart transplantation. The diagnosis is established via identification of virus by immunofluorescent monoclonal antibody staining or Tzanck smear; cultures and rising anti-HSV antibody titers may also be used. Treatment with acyclovir should be initiated and continued for 2 to 3 weeks. Most epidermal lesions respond to topical therapy, but any evidence of disseminated disease require

high-dose IV acyclovir and minimization of immunosuppression.

Infection associated with EBV is commonly detectable in the posttransplant period in solid-organ transplant recipients. The most common manifestations of EBV infection include the typical mononucleosis-type syndrome, pneumonitis, and hepatitis.⁶⁷ Diagnosis of EBV infection is made by detection of heterophile immunoglobulin (Ig)M antibody in serum or by following titers of antibodies to viral capsid antigen or early antigens. Polymerase chain reaction is also used to monitor viral activity and response to therapy. Treatment with acyclovir should be undertaken (or ganciclovir when CMV infection is also suspected). Severe invasive disease is also treated with reduction in immunosuppressive therapy. The most important aspect of EBV is its association with post-transplant lymphoproliferative disorder (PTLD), which is discussed below.

Varicella-zoster virus commonly will emerge from latency in immunosuppressed transplant patients to cause an episode of shingles.⁶⁸ Rarely, VZV may cause disseminated infections such as pneumonitis and encephalitis. The highest risk of disseminated VZV disease is in pediatric transplant patients who experience primary infection, which, in this population, has an associated 11% mortality.⁶⁹ Fortunately, the introduction of the varicella vaccine has markedly reduced this morbidity and mortality, and it is recommended for all pediatric and nonimmune transplant recipients prior to transplantation.⁷⁰ Varicella-Zoster virus infections are treated with acyclovir with reduction in immunosuppression for severe disseminated disease.⁷¹ There is no evidence supporting the efficacy of anti-VZV immune globulin in the treatment of severe VZV disease in the immunocompromised patient,⁶⁹ although it should be administered to seronegative solid organ transplant patients who are exposed to individuals with active VZV infection.

The role of HHV-6 as a cause of clinical disease has yet to be clearly established in solid-organ transplant patients. There is considerable evidence, primarily in bone marrow transplant and stem cell transplant patients, that points to an association between HHV-6 and disease, including neurologic syndromes, pneumonitis, and a mononucleosis-like immunosuppressive syndrome that may predispose to other opportunistic infections,^{72,73} but clear data are not yet available in solid-organ transplant recipients. There are reports of association of HHV-6 activation with severe CMV disease,^{74,75} but understanding cause and effect in this situation has been fraught with difficulty. Human herpes virus-7 and HHV-8 are not yet clearly associated with clinical syndromes that pose major problems in solid organ transplantation; however, data continue to be accumulated.

Several other viruses cause significant morbidity and mortality in solid-organ transplant patients. Adenoviral infection, although more common in bone marrow and stem cell transplant patients, does occur in solid-organ transplant recipients. Invasive adenoviral infection most commonly manifests as pneumonitis or hepatitis, both of which are associated with

poor prognosis.⁷⁶ Primary infection with human immunodeficiency virus (HIV) via organ transplant from an HIV-seropositive donor has been described, and HIV seropositive status is a contraindication to organ donation.⁷⁷ Until recently, HIV infection has been considered a contraindication to undergoing transplantation, but with the success of long-term multidrug therapy for HIV there has been some rethinking of this stance although doing so has not gained widespread acceptance.⁷⁸ Human papilloma viruses may cause disease through the development of tissue-specific growth leading to benign or malignant processes, including potentially cervical cancer, cancer of the vulva and perineum, condyloma acuminatum, laryngeal polyposis, and nonmelanotic skin cancer. Respiratory syncytial virus may produce a fulminant pneumonia in both adult and pediatric transplant patients. This diagnosis is made by examination of nasopharyngeal washings, and more severe cases may be treated with ribavirin.

Parasitic Infections

Several common parasitic infections are seen in immunosuppressed solid-organ transplant patients. *Pneumocystis carinii* is a common cause of pneumonia in immunosuppressed patients. *Pneumocystis carinii* pneumonia (PCP) is associated with profound defects in cellular immunity and normally is seen with CD4+ T cell counts lower than 200/ μ L.⁷⁹ These indices are often seen with OKT3 therapy for acute rejection. Prophylaxis with TMP-SMX makes this a rare entity; however, patients who do not receive prophylaxis due to allergy or noncompliance should be promptly evaluated for PCP should they present with respiratory illness, as untreated PCP has a high mortality. Diagnosis is typically made by bronchoscopy and broncho-alveolar lavage (BAL) with methenamine-silver stain of washings or by transbronchial biopsies. The characteristic alveolar and interstitial changes seen on chest radiograph are late findings and a normal film should not delay further evaluation and therapy. Empirical therapy is normally started prior to established diagnosis with IV TMP-SMX or inhaled pentamidine. Dapsone is also used in patients with sulfa sensitivity. Concurrent CMV infection is common, and CMV investigative studies should be undertaken in patients who fail to respond promptly to appropriate therapy for PCP.

Toxoplasma gondii is seen in immunosuppressed transplant patients, presenting as brain abscess with neurologic changes.⁸⁰ This entity is seen late in the posttransplant period, while brain abscess presenting in the early posttransplant period is more likely to be fungal.⁸¹ Cardiac transplant patients seem to be at greatest risk, possibly due to the presence of *T. gondii* cysts in donor myocardial tissue. Transplantation from cardiac allograft donors who are seropositive for *T. gondii* is normally accompanied by prophylactic treatment with pyrimethazine and sulfadiazine for 3 to 6 months. Treatment is with pyrimethazine and sulfadiazine, and mortality is high in patients with established CNS abscesses.

Posttransplant Lymphoproliferative Disorders

Posttransplant lymphoproliferative disorders' encompass a broad range of pathologies from simple lymphoid hyperplasia to aggressive monoclonal B-cell lymphomas. Epstein-Barr virus infection plays a central role in the etiology of these disorders, accounting for the inclusion here in a discussion of infectious complications of transplantation. In particular, primary EBV infection occurring after transplantation and immunosuppression has been associated with a markedly increased risk for the development of PTLTD.^{82,83} Other risk factors include active CMV disease,⁸⁴ CMV D+/R- mismatch,⁸² increasing intensity of immunosuppression,^{85,86} and possibly hepatitis C virus infection⁸⁷ and recipient cytokine gene polymorphisms.⁸⁸ Posttransplant lymphoproliferative disease are least common in adult renal transplant recipients and most common in children receiving small-bowel allografts, with pancreas and kidney-pancreas transplant patients exhibiting intermediate risk (chapter 9.2.5). Posttransplant lymphoproliferative disorders most commonly occur early after transplantation, concurrent with the most intense immunosuppression and with the use of anti-T cell therapy for acute rejection. However, a subset of PTLTD occurs late (several years) after transplant. These late-occurring neoplasms appear to be related more to patient age, duration and intensity of immunosuppression, and type of graft than to the more typical risk factors seen in early onset disease.

The clinical presentation of PTLTD varies widely, as might be expected from the wide range of pathology encountered with this entity. Many patients will experience fever, sweats, and myalgias as the only symptoms. Weight loss, diarrhea, and symptoms of upper-respiratory infection are also common. Some but not all will develop lymphadenopathy. Central nervous system involvement, which occurs in up to 20% of cases,⁸⁹ will often manifest as mental status changes. Gastrointestinal disease may be silent or may present as abdominal pain, GI bleeding, perforation with peritonitis, or bowel obstruction. Intrathoracic PTLTD has a characteristic radiographic appearance of multiple circumscribed pulmonary nodules that may or may not be accompanied by mediastinal lymphadenopathy. Posttransplant lymphoproliferative disorder in the allograft itself can present similarly to acute rejection, and making this diagnosis correctly on biopsy is essential as the therapeutic approach to these two entities is diametrically opposite, one from the other.

Biopsy of the lesion is the gold standard in making the diagnosis of PTLTD. Biopsy specimens are histologically graded based on cell morphology and nodal architecture and assessed for clonality and EBV positivity. Special stains are used to identify cell origin. Biopsies should be reviewed by pathologists familiar with PTLTD as well as with allograft rejection and opportunistic infection with reference to consensus conference standards for the grading and classification of

PTLD.⁹⁰ Histological classification is at present by the Harris standard formulation.⁹¹ Epstein-Barr virus serology does not typically add to the diagnostic work-up of PTLD, with many false negatives in established primary EBV infection.^{92,93} Similarly, peripheral cytology is not helpful in making the diagnosis.⁹⁴ Patients suspected of harboring PTLD should have imaging of the head, thorax, and abdomen.

Currently, there are little clinical data directing the optimal prophylaxis regimen against PTLD. Clearly, it is important to identify the high-risk patients (children, liver and bowel transplant recipients, EBV-positive recipients, patients receiving intense anti-T-cell therapy for rejection) and monitor them closely. Similarly, OKT3 therapy should not be started in high-risk patients without a clear biopsy diagnosis of acute rejection. Both antiviral agents and passive immune transfer with anti-EBV immune globulin have been proposed as prophylaxis against PTLD, but data supporting these approaches is at present lacking. Several trials are ongoing to establish the best approach.⁹⁵ Intriguingly, the improvements in baseline immunosuppression preventing acute rejection appear to decrease the frequency of PTLD, likely by reducing the frequency of OKT3 or other cytolytic therapy.⁹⁶

Treatment of established PTLD is variable depending on the clinical situation and histological diagnosis of each individual patient. There are no trials to guide therapy; hence, a graded, individualized approach is taken. Ordinarily, immunosuppression is reduced to minimal levels and specific therapy directed at the neoplasm is instituted. Between 25% and 50% of patients will show regression of their PTLD after reduction in immunosuppression.^{97,98} Surgical intervention is clearly indicated for GI PTLD, which manifests as an acute abdomen. Surgical debulking of tumor burden has also been utilized in amenable cases,⁹⁹ as has radiotherapy.¹⁰⁰ Medical approaches to treating PTLD include antiviral medications,¹⁰¹ interferon- α ,^{102,103} immunoglobulins,^{83,101} standard, low-dose, and high-dose chemotherapy protocols,^{104,105} and—most recently—monoclonal antibodies directed against B-cell surface markers such as CD19 and CD20 (rituximab).^{106,107} In unusual cases, immunomodulatory therapy with adoptive transfer of cytotoxic T cells sensitized to EBV has been attempted with some success.¹⁰⁸ At present, there is no consensus approach to these challenging patients, and a graded, individualized approach is warranted until the issue is clarified by trials. Late-onset PTLD, occurring at greater than 1 to 2 years posttransplant will often not respond to the reduction in immunosuppression and medical therapy used in early onset disease. This neoplasm is often EBV negative and is difficult to treat due to the infectious complications of the aggressive chemotherapy that is often required. Similarly, CNS involvement may be a marker for potential refractoriness to therapy, possibly due to the relatively privileged immune site. Treatment options here include intrathecal administration of interferon- α and anti-B cell antibody therapy along with local radiotherapy, but the prognosis remains guarded.^{89,109}

References

1. International Pancreas Transplant Registry Newsletter. 2002; 14:4–24.
2. Smets YF, van der Pijl JW, van Dissel JT, et al. Infectious disease complications of simultaneous pancreas kidney transplantation. *Nephrol Dial Transplant* 1997;12:764–771.
3. Dunn DL, Acton RD. Solid organ transplantation. In: Armstrong D, Cohen J, eds. *Infectious Diseases*. London: Mosby International; 1999:3.1–3.16.
4. Dunn DL. Problems related to immunosuppression: Infection and malignancy occurring after solid organ transplantation. *Crit Care Clin* 1990;6:955–977.
5. Brayman KL, Stephanian E, Matas AJ, et al. Analysis of infectious complications occurring after solid-organ transplantation. *Arch Surg* 1992;127:38–48.
6. Dummer JS, Hardy A, Poorsattar A, et al. Early infections in kidney, heart, and liver transplant recipients on cyclosporine. *Transplantation* 1983;36:259–267.
7. Snyderman DR. Epidemiology of infections after solid-organ transplantation. *Clin Infect Dis* 2001;33:S5–S8.
8. Fryd DS, Peterson PK, Ferguson RM, et al. Cytomegalovirus as a risk factor in renal transplantation. *Transplantation* 1980; 30:436–439.
9. Dunn DL, Matas AJ, Fryd DS, et al. Association of concurrent herpes simplex virus and cytomegalovirus with detrimental effects after renal transplantation. *Arch Surg* 1984;119:812–817.
10. Singh N, Carrigan DR. Human herpes virus-6 in transplantation: An emerging pathogen. *Ann Intern Med* 1996;124:1065–1071.
11. McGrath D, Falagas ME, Freeman R, et al. Adenovirus infection in adult orthotopic liver transplant recipients: Incidence and clinical significance. *J Infect Dis* 1998;177:459–462.
12. McCormick WF, Schochet SS Jr, Sarles HE, et al. Progressive multifocal leukoencephalopathy in renal transplant recipients. *Arch Intern Med* 1976;136:829–834.
13. Feldhoff CM, Balfour HH, Simmons RL, et al. Varicella in children with renal transplants. *J Pediatr* 1981;98:25–30.
14. Preiksaitis JK, Diaz-Mitoma F, Mirzayans F, et al. Quantitative oropharyngeal Epstein-Barr virus shedding in renal and cardiac transplant recipients: relationship to immunosuppressive therapy, serologic responses, and the risk of post-transplant lymphoproliferative disorder. *J Infect Dis* 1996;166:986–994.
15. Lumberas C, Cuervas-Mons V, Jara P, et al. Randomized trial of fluconazole versus nystatin for the prophylaxis of *Candida* infection following liver transplantation. *J Infect Dis* 1996;174: 582–588.
16. Kusne S, Torre-Cisneros J, Manez R, et al. Factors associated with invasive lung aspergillosis and the significance of positive *Aspergillus* culture after liver transplantation. *J Infect Dis* 1992;166:1379–1383.
17. Cohen IM, Galgiani JN, Potter D, Ogden DA. Coccidiomycosis in renal replacement therapy. *Arch Intern Med* 1982;142: 489–494.
18. Wheat LJ, Smith EJ, Sathapatayavongs B, et al. Histoplasmosis in renal allograft recipients: Two large urban outbreaks. *Arch Intern Med* 1983;143:703–707.
19. Spees EK, Light JA, Oakes DD, et al. Experiences with ca-

- daver renal allograft contamination before transplantation. *Br J Surg* 1982;69:482–485.
20. Prat V, Horciekova M, Matousovic M, Liska M. Urinary tract infection in renal transplant patients. *Infection* 1985;13:207–210.
 21. Konigsrainer A, Steurer W, Aichberger C, et al. Low incidence of urinary tract infection after combined kidney and segmental pancreas transplantation with bladder drainage. *Transplant Proc* 1992;24:784–785.
 22. Lapchik MS, Castelo-Filho A, Pestana JO, et al. Risk factors for nosocomial urinary tract and postoperative wound infections in renal transplant patients: A matched-pair case-control study. *J Urol* 1992;147:994–998.
 23. Nicol DN, P'Ng K, Hardie DR, et al. Routine use of indwelling ureteral stents in renal transplantation. *J Urol* 1993;150:1375–1379.
 24. Tolkoff-Rubin NE, Cosimi AB. A controlled study of trimethoprim-sulfamethoxazole prophylaxis of urinary tract infection in renal transplant recipients. *Rev Infect Dis* 1982;4:614.
 25. Rabito FJ, Pankey GA. Infections in orthotopic heart transplant patients at the Ochsner Medical Institutions. *Med Clin North Am* 1992;76:1125–1134.
 26. Kramer MR, Marshall SE, Starnes VA, et al. Infectious complications in heart-lung transplantation: Analysis of 200 episodes. *Arch Intern Med* 1993;153:2010–2016.
 27. Everett J, Wahoff DC, Statz C, et al. Characterization and impact of wound infection after pancreas transplantation. *Arch Surg* 1994;129:1310–1317.
 28. Hesse UJ, Sutherland DER, Simmons RL, et al. Intraabdominal infections in pancreas transplant recipients. *Ann Surg* 1986;203:153–162.
 29. Freise CE, Stock PG, Roberts JP, Melzer JS. Low postoperative wound infection rates are possible following simultaneous pancreas-kidney transplantation. *Transplant Proc* 1995;27:3069–3070.
 30. Knight RJ, Bodian C, Rodriguez-Laiz G, et al. Risk factors for intra-abdominal infection after pancreas transplantation. *Am J Surg* 2000;179:99–102.
 31. Benedetti E, Troppmann C, Gruessner AC, et al. Pancreas graft loss caused by intra-abdominal infection. *Arch Surg* 1996;131:1054–1060.
 32. Mermel LA, Maki DG. Bacterial pneumonia in solid organ transplantation. *Sem Respir Infect* 1990;5:10–29.
 33. Deusch E, End A, Grimm M, et al. Early bacterial infections in lung transplant recipients. *Chest* 1993;104:1412–1416.
 34. Sinnot JT, Emmanuel PJ. Mycobacterial infections in the transplant patient. *Sem Respir Infect* 1990;5:65–73.
 35. Stamm AM, Dismukes WE, Simmons BP, et al. Listeriosis in renal transplant recipients: Report of an outbreak and review of 102 cases. *Rev Infect Dis* 1982;2:S264–S269.
 36. Chapman SW, Wilson JP. Nocardiosis in transplant recipients. *Sem Respir Infect* 1990;5:74–79.
 37. Paya CV. Fungal infections in solid organ transplantation. *Clin Infect Dis* 1993;16:677–688.
 38. Nieto-Rodriguez JA, Kusne S, Manez R, et al. Factors associated with the development of candidemia and candidemia-related death among liver transplant recipients. *Ann Surg* 1996;223:70–76.
 39. Arathoon EG, Gotuzzo E, Noriega LM. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiasis. *Antimicrob Agents Chemother* 2002;46:451–457.
 40. Villanueva A, Arathoon EG, Gotuzzo E. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. *Clin Infect Dis* 2001;33:1529–1535.
 41. Kusne S, Torre-Cisneros J, Manez R, et al. Factors associated with invasive lung aspergillosis and the significance of positive *Aspergillus* culture after liver transplantation. *J Infect Dis* 1992;166:1379–1383.
 42. Denning DW, Lee JY, Hostetler JS, et al. NIAID mycoses study group multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med* 1994;97:135–144.
 43. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: Review of 2121 published cases. *Rev Infect Dis* 1990;12:1147–1201.
 44. Watson AJ, Russell RP, Cabreja RF, et al. Cure of cryptococcal infection during continued immunosuppressive therapy. *Q J Med* 1985;55:169–172.
 45. Cohen KM, Galgiani JN, Potter D, Ogden DA. Coccidiomycosis in renal replacement therapy. *Arch Intern Med* 1982;142:489–494.
 46. Davies SF, Sarosi GA, Peterson PK, et al. Disseminated histoplasmosis in renal transplant recipients. *Am J Surg* 1979;137:686–691.
 47. Jimenez C, Lumbreras C, Aguado JM, et al. Successful treatment of mucor infection after liver or pancreas-kidney transplantation. *Transplantation* 2002;73:476–480.
 48. Dunn DL, Mayoral JL, Gillingham KJ, et al. Treatment of invasive cytomegalovirus disease in solid organ transplant patients with ganciclovir. *Transplantation* 1991;51:98–106.
 49. van der Bij W, Speich R. Management of cytomegalovirus infection and disease after solid organ transplantation. *Clin Infect Dis* 2001;33:S33–S37.
 50. Dunn DL, Najarian JS. New approaches to the diagnosis, prevention, and treatment of cytomegalovirus infection after transplantation. *Am J Surg* 1991;161:250–255.
 51. Gleaves CA, Smith TF, Shuster EA, Pearson GR. Comparison of standard tube and shell vial cell culture techniques for the detection of cytomegalovirus in clinical specimens. *J Clin Microbiol* 1985;21:217–221.
 52. Erice A, Holm MA, Gill PC, et al. Cytomegalovirus (CMV) antigenemia assay is more sensitive than shell vial cultures for rapid detection of CMV in polymorphonuclear blood leukocytes. *J Clin Microbiol* 1992;30:2822–2825.
 53. The TH, van der Ploeg M, van den Berg AP, et al. Direct detection of cytomegalovirus in peripheral blood leukocytes—a review of the antigenemia assay and polymerase chain reaction. *Transplantation* 1992;54:193–198.
 54. Dunn DL, Gillingham KJ, Kramer MA, et al. A prospective, randomized study of acyclovir versus ganciclovir plus human immune globulin prophylaxis of cytomegalovirus infection after solid organ transplantation. *Transplantation* 1994;57:876–884.
 55. Rubin RH, Kemmerly SA, Conti D, et al. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. *Transplant Infect Dis* 2000;2:112–117.
 56. Flechner SM, Avery RK, Fisher R, et al. A randomized prospective controlled trial of oral acyclovir versus oral ganciclovir for

- cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998;66:1682–1688.
57. Winston DJ, Wirin D, Shaked A, Busuttill RW. Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995;346:69–74.
 58. Rayes N, Seehofer D, Schmidt CA, et al. Prospective randomized trial to assess the value of preemptive oral therapy for CMV infection following liver transplantation. *Transplantation* 2001;72:881–885.
 59. Singh N, Paterson DL, Gayowski T, et al. Cytomegalovirus antigenemia directed pre-emptive prophylaxis with oral versus I.V. ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients: A randomized, controlled trial. *Transplantation* 2000;70:717–722.
 60. Brennan DC, Garlock KA, Lippmann BA, et al. Control of cytomegalovirus-associated morbidity in renal transplant patients using intensive monitoring and either preemptive or deferred therapy. *J Am Soc Nephrol* 1997;8:118–125.
 61. Merigan TC, Renlund DG, Keay S, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. *N Engl J Med* 1992;326:1182–1186.
 62. Hertz MI, Jordan C, Savik SK, et al. Randomized trial of daily versus three-times-weekly prophylactic ganciclovir after lung and heart-lung transplantation. *J Heart Lung Transplant* 1998;17:913–920.
 63. Jacobsen N, Schafer U, Ostendorf P, et al. Intravenous hyperimmune globulin prophylaxis against cytomegalovirus interstitial pneumonitis after allogeneic bone marrow transplantation. *Tokai J Exp Clin Med* 1985;10:193–195.
 64. Ruutu T, Ljungman P, Brinch L, et al. No prevention of cytomegalovirus infection by anti-cytomegalovirus hyperimmune globulin in seronegative bone marrow transplant recipients. The Nordic BMT Group. *Bone Marrow Transplant* 1997;19:233–236.
 65. Studies of Ocular Complications of AIDS. Cytomegalovirus (CMV) culture results, drug resistance, and clinical outcome in patients with AIDS and CMV retinitis treated with foscarnet or ganciclovir. Studies of Ocular Complications of AIDS (SOCA) in collaboration with the AIDS Clinical Trial Group. *J Infect Dis* 1997;176:50–58.
 66. Carrier M, Pelletier GB, Cartier R, et al. Prevention of herpes simplex virus infection by oral acyclovir after cardiac transplantation. *Can J Surg* 1992;35:513–516.
 67. Langnas AN, Castaldo P, Markin RS, et al. The spectrum of Epstein-Barr virus infection with hepatitis following liver transplantation. *Transplant Proc* 1991;23:1513–1514.
 68. Straus SE, Ostrove JM, Inchauspe G, et al. Varicella-zoster infections: Biology, natural history, treatment, and prevention. *Ann Intern Med* 1988;108:221–237.
 69. Lynfield R, Herrin JT, Rubin RH. Varicella in pediatric renal transplant recipients. *Pediatrics* 1992;90:216–220.
 70. Gershon AA. Immunizations for pediatric transplant patients. *Kidney Int* 1993;43(suppl):S87–S90.
 71. Anderson DJ, Jordan MC. Viral pneumonia in recipients of solid organ transplants. *Sem Respir Infect* 1990;5:38–49.
 72. Zerr DM, Gupta D, Huang ML, et al. Effect of antivirals on human herpes virus 6 replication in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2002;34:309–317.
 73. Buchbinder S, Elmaagacli AH, Schaefer UW, Roggendorf M. Human herpes virus 6 is an important pathogen in infectious lung disease after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2000;26:639–644.
 74. DesJardin JA, Cho E, Supran S, et al. Association of human herpes virus 6 reactivation with severe cytomegalovirus-associated disease in orthotopic liver transplant recipients. *Clin Infect Dis* 2001;33:1358–1362.
 75. Lautenschlager I, Linnavuori K, Lappalainen M, et al. HHV-6 reactivation is often associated with CMV infection in liver transplant patients. *Transplant Int* 2000;13:S351–S353.
 76. Carrigan DR. Adenovirus infections in immunocompromised patients. *Am J Med* 1997;102:71–74.
 77. Simonds RJ. HIV transmission by organ and tissue transplantation. *AIDS* 1993;7(suppl 2):S35–S38.
 78. Ahuja TS, Zingman B, Glicklich D. Long-term survival in an HIV-infected renal transplant recipient. *Am J Nephrol* 1997;17:480–482.
 79. Gluck T, Geerdes-Fenge HF, Straub RH, et al. *Pneumocystis carinii* pneumonia as a complication of immunosuppressive therapy. *Infection* 2000;28:227–230.
 80. Luft BJ, Naot Y, Araujo FG, et al. Primary and reactivated toxoplasma infection in patients with cardiac transplants. *Ann Intern Med* 1983;99:27–31.
 81. Selby R, Ramirez CB, Singh R, et al. Brain abscess in solid organ transplant recipients receiving cyclosporine-based immunosuppression. *Arch Surg* 1997;132:304–310.
 82. Walker RC, Marshall WF, Strickler J, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis* 1995;20:1346–1353.
 83. Ellis D, Jaffe R, Green M, et al. Epstein-Barr virus-related disorders in children undergoing renal transplantation with tacrolimus-based immunosuppression. *Transplantation* 1999;68:997–1003.
 84. Manez R, Breinig MC, Linden P, et al. Posttransplant lymphoproliferative disease in primary Epstein-Barr virus infection after liver transplantation: The role of CMV disease. *J Infect Dis* 1997;176:1462–1467.
 85. Cox KL, Lawrence-Miyasaki LS, Garcia-Kennedy R, et al. An increased incidence of Epstein-Barr virus infection and lymphoproliferative disorder in young children on FK506 after liver transplantation. *Transplantation* 1995;59:524–529.
 86. Keay S, Oldach D, Wiland A, et al. Post-transplant lymphoproliferative disorder associated with OKT3 and decreased antiviral prophylaxis in pancreas transplant recipients. *Clin Infect Dis* 1998;26:596–600.
 87. McLaughlin K, Wajstaub S, Marotta P, et al. Increased risk for posttransplant lymphoproliferative disease in recipients of liver transplants with hepatitis C. *Liver Transplant* 2000;6:570–574.
 88. Helminen M, Lahdenpohja N, Hurme M. Polymorphism of the interleukin-10 gene is associated with susceptibility to Epstein-Barr virus infection. *J Infect Dis* 1999;180:496–499.
 89. Penn I, Porat G. Central nervous system lymphomas in organ allograft recipients. *Transplantation* 1995;59:240–244.
 90. Paya C, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced post-transplant lymphoproliferative disorders. *Transplantation* 1999;68:1517–1525.
 91. Harris NL, Fery JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: Summary of Society for Hematopathology workshop. *Sem Diagn Pathol* 1997;14:8–14.
 92. Cen H, Williams PA, McWilliams HP, et al. Evidence for restricted Epstein-Barr virus latent gene expression and anti-EBNA antibody response in solid organ transplant recipients

- with posttransplant lymphoproliferative disorders. *Blood* 1993;81:1393–1403.
93. Riddler SA, Breinig MC, McKnight JLC. Increased levels of circulating Epstein-Barr virus (EBV)-infected lymphocytes and decreased EBV nuclear antigen antibody responses are associated with the development of posttransplant lymphoproliferative disease in solid organ transplant recipients. *Blood* 1994;84:972–974.
 94. Davey DD, Gulley ML, Walker WP, Zaleski S. Cytologic findings in posttransplant lymphoproliferative disease. *Acta Cytol* 1990;34:304–310.
 95. Green M, Reyes J, Webber S, Rowe D. The role of antiviral and immunoglobulin therapy in the prevention of Epstein-Barr virus infection and post-transplant lymphoproliferative disease following solid organ transplantation. *Transplant Infect Dis* 2001;3:97–103.
 96. Birkeland SA, Andersen HK, Hamilton-Dutoit SJ. Preventing acute rejection, Epstein-Barr virus infection, and posttransplant lymphoproliferative disorders after kidney transplantation: Use of acyclovir and mycophenolate mofetil in a steroid-free immunosuppressive protocol. *Transplantation* 1999;67:1209–1214.
 97. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporine–steroid therapy. *Lancet* 1984;1:584–587.
 98. Penn I. Immunosuppression: A contributory factor in lymphoma formation. *Clin Transplant* 1992;6:214–219.
 99. Cacciarelli TV, Green M, Jaffe R, et al. Management of post-transplant lymphoproliferative disease in pediatric liver transplant recipients receiving tacrolimus (FK506) therapy. *Transplantation* 1998;66:1047–1052.
 100. Koffman BH, Kennedy AS, Heyman M, et al. Use of radiation therapy in posttransplant lymphoproliferative disorder (PTLD) after liver transplantation. *Int J Cancer* 2000;90:104–109.
 101. Pirsch JD, Stratta RJ, Sollinger HW, et al. Treatment of severe Epstein-Barr virus-induced lymphoproliferative syndrome with ganciclovir. *Am J Med* 1989;86:241–244.
 102. Shapiro RS, Chauvenet A, McGuire W, et al. Treatment of B-cell lymphoproliferative disorders with interferon alfa and intravenous gamma-globulin. *N Engl J Med* 1988;318:1334.
 103. Cantarovitch M, Barkun JS, Forbes RDC, et al. Successful treatment of post-transplant lymphoproliferative disorder with interferon-alpha and intravenous immunoglobulin. *Clin Transplant* 1998;12:109–115.
 104. Garrett TJ, Chadburn A, Barr ML, et al. Posttransplantation lymphoproliferative disorders treated with cyclophosphamide–doxorubicin–vincristine–prednisone chemotherapy. *Cancer* 1993;72:2782–2785.
 105. Smets F, Vajro P, Cornu G, et al. Indications and results of chemotherapy in children with posttransplant lymphoproliferative disease after liver transplantation. *Transplantation* 2000;69:982–984.
 106. Schaar CG, van der Pijl JW, van Hoek B, et al. Successful outcome with a “quintuple approach” of posttransplant lymphoproliferative disorder. *Transplantation* 2001;71:47–52.
 107. Faye A, Quartier P, Reguerre Y. Chimeric anti-CD20 monoclonal antibody (rituximab) in post-transplant B-lymphoproliferative disorder following stem cell transplantation in children. *Br J Haematol* 2001;115:112–118.
 108. Rooney CM, Smith CA, Ng CY, et al. Use of gene-modified virus-specific T lymphocytes to control Epstein-Barr virus-related lymphoproliferation. *Lancet* 1995;345:9–13.
 109. Stephan JL, Le Deist F, Blanche S, et al. Treatment of central nervous system B lymphoproliferative syndrome by local infusion of a B cell-specific monoclonal antibody. *Transplantation* 1992;54:246–249.

9.2.4

Nonimmunologic Endocrine Graft Dysfunction

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The effect of the host alloimmune response on graft function and survival has been extensively studied. (See chapters 9.2.2, 11, and 13.1 for information on temporary or chronic endocrine graft dysfunction due to acute or chronic rejection, recurrence of autoimmune type 1 diabetes, vascular complications, infection, or graft pancreatitis.) But, relatively little attention has been paid to endocrine graft dysfunction due to causes *other* than rejection or recurrence of autoimmune diabetes.

Endocrine graft dysfunction manifests most commonly as hyperglycemia and, more rarely, as hypoglycemia. Note that the term “endocrine graft dysfunction” may be a misnomer because causes not primarily related to the graft itself may lead to hyperglycemia (e.g., administration of diabetogenic drugs, new development of an insulin-resistant state) or hypoglycemia (e.g., insulin autoantibodies).

Adequate pancreas graft function can be stringently defined by fasting blood glucose levels in the normal range without any need for supplemental exogenous insulin or oral hypoglycemic agents. Conversely, pancreas graft nonfunction can be defined by the need for supplemental insulin or oral hypoglycemic agents to maintain glucose levels in a normal or near-normal range. Such clear-cut definitions ignore pancreas recipients who might still derive some benefit from a partially functioning graft (e.g., avoidance of ketoacidotic complications without requiring insulin). Nonetheless, they reflect the standards used for outcome analysis of other solid-organ grafts. Similar standards should, ideally, also be applied to other modalities of insulin replacement therapy, such as islet allotransplants.¹

Hyperglycemia

Primary Nonfunction

Primary nonfunction is well defined and routinely reported for other solid-organ transplants, such as the kidney and liver. But,

its true incidence for pancreas transplants remains unknown. Primary nonfunction is typically defined by the absence of graft function after other causes of early graft failure (e.g., vascular graft thrombosis, hyperacute rejection) have been ruled out. For pancreas transplants, primary nonfunction entails the permanent need for insulin posttransplant. In the recent literature, only one study directly addresses this issue.² According to that large, single-center series of 1,084 pancreas transplants, the incidence of primary nonfunction was 0.5% and advanced donor age was identified as a risk factor.² In contrast, one case report of a pancreas recipient who never became insulin-independent posttransplant described the problem as posttransplant type 2 diabetes.³ That case study illustrates the difficulties associated with diagnosing primary nonfunction and the lack of a widely accepted definition in the field.

It is a matter of speculation whether the incidence of primary nonfunction after pancreas transplants is truly as low as reported (0.5%). If it is that low, the reason may be the more stringent selection criteria for pancreas donors as compared with other solid-organ donors. In addition, primary nonfunction of other solid-organ grafts usually correlates with longer preservation times and the use of older donors. However, those two donor-related risk factors for primary nonfunction of extrapancreatic solid-organ grafts are also significant risk factors for early technical failure of pancreas grafts.⁴ It may be that pancreas grafts fail because of technical complications (e.g., graft thrombosis, infection) before primary nonfunction can even be diagnosed.

Other causes of early pancreas graft nonfunction (e.g., hyperacute rejection, graft thrombosis) can be ruled out if C-peptide, insulin, and proinsulin levels are elevated and if the proinsulin-to-insulin ratio is elevated. In one report of two pancreas recipients who never achieved insulin independence (and whose grafts would thus fulfill the stringent definition of primary nonfunction), fasting proinsulin levels were ele-

vated, indicative of premature insulin release due to metabolic stress. However, it is unclear whether such laboratory findings predict irreversible graft loss.⁵

Delayed Endocrine Graft Function

For extrapancreatic solid-organ grafts, delayed endocrine graft function requires a temporary substitute for, or medical support of, the recovering graft: posttransplant dialysis (for kidney transplants), plasmatic coagulation factors (liver), or inotropic agents (heart). Surprisingly, for pancreas transplants delayed endocrine graft function has received little attention. The few reports that address this phenomenon describe a variable incidence.^{6–8}

In general, delayed endocrine graft function can be defined by a temporary discrepancy, early posttransplant, between the graft's functional, physiological capacity and the recipient's functional, physiological needs. For most solid-organ grafts, the recipient's physiological demands are not significantly higher immediately posttransplant as compared with the period after hospital discharge. For example, kidney and heart grafts do not face a significantly different "workload" over time (except for the consequences of the hypermetabolic–hyperdynamic state induced by the transplant operation itself).

But, pancreas grafts are unique with regard to their workload over time. Besides the usual sequelae of procurement and preservation, pancreas grafts face an organ-specific host of factors that antagonize the restitution of early posttransplant euglycemia. Obesity and dyslipidemia (caused by diabetes) can increase insulin resistance. Uremia, as present in simultaneous pancreas–kidney recipients with end-stage diabetic nephropathy, can also increase insulin resistance. Recipients with systemic venous graft drainage have hyperinsulinemia. Metabolic control after systemic venous drainage and after portal venous drainage of the pancreas graft effluent is equally adequate; nevertheless, an overall higher amount of insulin may be necessary after systemic venous drainage to achieve the same metabolic effect, effectively increasing the metabolic stress on the pancreas.

Further, the denervation of the pancreas graft may—at least hypothetically—impair posttransplant secretory responses. The consequences of the transplant operation itself, and its resultant stress and hyperglucagonemia, can increase the demand for insulin. So can infusion of glucose-containing solutions or total parenteral nutrition. In addition, prednisone, cyclosporine, and tacrolimus, all administered posttransplant, decrease glucose tolerance and can have adverse effects on the islets themselves. Moreover, diminished insulin secretion (as in the case of a pancreas graft recovering from ischemia–reperfusion injury) can in itself decrease sensitivity to insulin, independent of concomitant hyperglycemia.

Given this vast array of factors working against the endocrine allopancreas, in particular, early posttransplant (e.g., due to high-dose steroids, slowly resolving uremia), it is surprising that so few detailed reports address the quality of immediate endocrine graft function. Delayed endocrine graft function rates of 3% to 69% have been reported.^{6–8} However,

all but one⁸ of those reports did not specify the indications for, or the doses and duration of, insulin administration.^{6,7}

The one exception did address insulin administration in a more systematic fashion: In that report, blood glucose levels were maintained below 150 mg/dL for the first 2 weeks posttransplant using continuous insulin infusion as necessary.⁸ Delayed endocrine graft function was defined by the amount of insulin needed to achieve that metabolic goal. With continuous insulin infusion (akin to a variation of the euglycemic hyperinsulinemic clamp technique), the incidence of delayed endocrine graft function was relatively high: 69%. It was associated with pretransplant recipient weight > 80 kg, donor age over 45, and cardiocerebrovascular and nontraumatic causes of donor death. Interestingly, the incidence of acute pancreas rejection episodes was similar for recipients with and without delayed endocrine graft function. In contrast, past studies of kidney recipients have shown that delayed graft function is associated with a higher incidence of rejection.⁹ Nevertheless, in the continuous-infusion study, pancreas graft survival at 3 years was significantly lower for recipients with delayed graft function. The study's authors concluded that the increased rate of pancreas graft failure after delayed endocrine graft function was a consequence of insufficient functional reserve (e.g., older donors), rather than of increased immunogenicity. Of note, in simultaneous pancreas–kidney recipients delayed function of the pancreas did not correlate with delayed function of the simultaneously transplanted kidney. Thus, pretransplant reduction of recipient weight and careful donor selection are important to optimize early posttransplant endocrine graft function.⁸

Clearly, additional investigations in this vastly underexplored field are necessary. Reliable methods must be developed to assess endocrine graft function of the donor pancreas *before* explantation. Also crucial is assessment of the recipient's overall endocrine requirements (including the sum of insulin resistance and the derangement of glucose homeostasis caused by immunosuppressants). Functional matching of a donor and recipient pretransplant would allow expansion of the donor pool and further improve long-term outcome of pancreas transplants.

Late Pancreas Graft Dysfunction

Even less is known about the true incidence and causes of late (> 4 weeks posttransplant) endocrine dysfunction secondary to causes other than acute or chronic rejection and recurrence of type 1 diabetes (Table 9.2.4.1).

Isolated case reports have been published about pancreas recipients who developed type 2 diabetes posttransplant with and without any identifiable cause (e.g., new onset of obesity).^{3,10,11} Administration of diabetogenic drugs may play a role. Theoretically, it is also possible that a cadaver pancreas donor was destined to develop type 2 diabetes later in life. Pancreases from such donors may be more prone to dysfunction in the recipient, in particular when placed under pharmacological (e.g., corticosteroids) or immunologic (e.g., re-

TABLE 9.2.4.1. Causes of late endocrine graft dysfunction resulting in hyperglycemia.

Chronic rejection
Late acute rejection
Graft pancreatitis
New onset of type 2 diabetes
Insulin-resistant state
Impaired insulin secretion
Drug side effects
Corticosteroids
Calcineurin inhibitors
Tacrolimus
Cyclosporine
Vascular complications
Late graft thrombosis (arterial > venous)
Arteriovenous fistula
Mycotic pseudoaneurysm
Preanastomotic arterial stenosis
Intragraft atherosclerosis and stenosis
Graft arterial aneurysm
Recurrence of type 1 diabetes
Infections
Systemic
Local (e.g., intra- or perigraft abscess)

jection) stress. Pancreatitis and vascular complications pertaining to the recipient's or graft's vasculature may also on occasion be responsible for endocrine dysfunction (Table 9.2.4.1) (see also chapter 9.2.2).

Glucose intolerance with "normal" fasting C-peptide and free insulin levels, with or without elevated fasting proinsulin levels and an elevated proinsulin-to-insulin ratio, may indicate graft dysfunction under metabolic stress conditions.^{5,12} If acute or chronic rejection cannot be ruled out as a cause of the endocrine dysfunction, a pancreas biopsy may be indicated. In bladder-drained recipients, preserved urinary amylase production at or near baseline provides an additional means to differentiate nonimmunologic from immunologic late pancreas graft dysfunction.

Treatment of recipients with late endocrine dysfunction includes addressing the underlying cause if possible, (e.g., instituting a weight loss regimen). Selected recipients may benefit from steroid withdrawal and a switch from diabetogenic immunosuppressants (cyclosporine and tacrolimus) to those without notable impact on glucose metabolism (e.g., sirolimus). Medical treatment, as in any other type 2 diabetic patient, should aim at enhancing insulin secretion (e.g., with sulfonylureas), improving insulin action (e.g., with thiazolidinediones), and insulin administration, as necessary. Intensive treatment may even induce at least a transient remission of the endocrine graft dysfunction, according to one case report.¹³

The rare recipient who experiences isolated pancreatic exocrine burnout is a diagnostic and prognostic challenge. In bladder-drained normoglycemic pancreas recipients, burnout manifests as progressive and persistent loss of urinary amylase production in the absence of acute rejection. In the only reported case series, no endocrine abnormalities had been observed at the time burnout was diagnosed or during the relatively short

follow-up (mean, 20 months).¹⁴ Future studies with longer follow-up will need to investigate whether the observed dissociation between (decreased) exocrine and (stable) endocrine function predicts eventual late endocrine graft failure.

Hypoglycemia

About 25% to 50% of pancreas recipients report occasional *symptoms* of hypoglycemia, as late as several years post-transplant.^{15–19} A few studies have documented hypoglycemia in pancreas recipients reporting hypoglycemic symptoms.^{15,17,20,21} But, the significance of those findings is unclear because blood glucose levels were measured after an intravenous glucose pulse or a liquid meal rather than under "real-life" conditions.^{17,20} Moreover, hypoglycemia does not always correlate with clinical symptoms and can thus be asymptomatic.¹⁹ However, severe hypoglycemia that results in loss of consciousness or requires intervention is rare.

At least six different mechanisms have been proposed for hypoglycemia after pancreas transplantation. First, in recipients with systemic venous drainage hypoglycemia may be due to the absence of the hepatic first-pass effect of pancreatic hormones, resulting in increased uptake of glucose by muscle, decreased hepatic gluconeogenesis and glucose release, and systemic hyperinsulinemia.²²

Second, other investigators have suggested that an elevated insulin antibody titer may cause hypoglycemia.^{15,20,21} Anti-insulin antibodies may induce hypoglycemia by prolonging the half-life of circulating insulin, with the relatively large amount of antibody-bound insulin serving as a reservoir. After free insulin is cleared, it would be replaced by insulin dissociating from the circulating antibody, hence maintaining an inappropriately high free insulin concentration. Alternatively, the insulin bioactivity may be potentiated by the ability of the antibodies to cross-link insulin to the insulin receptors. Or, anti-insulin antibodies may be anti-idiotypic and capable of self-activating the insulin receptors.²¹

Third, partially defective counterregulatory responses to hypoglycemia may be involved. After a successful pancreas transplant, glucagon responses to hypoglycemia are restored to normal. In contrast, epinephrine secretion, which is partially defective in type 1 diabetics who undergo a pancreas transplant, improves but is not restored to the levels observed in nondiabetics during a hypoglycemic challenge.²³ These findings may explain the occasional manifestation of post-transplant hypoglycemia. Interestingly, in a recent report on two pancreas recipients with documented hypoglycemia the glucagon response to hypoglycemia was noted to be blunted.²⁴ The report's authors postulated that altered hepatic glucose production (seen in type 1 diabetics who do not undergo a transplant) persists posttransplant. However, their findings contradict the demonstration by other studies of (1) normalization of counterregulatory mechanisms to hyperglycemia, at least with respect to the glucagon response,^{23,25,26} and (2) normalization of hepatic glucose production.²⁷

Fourth, a more recent study postulated that the hypoglycemia seen in pancreas recipients may be a reactive postprandial hypoglycemia.¹⁵

Fifth, hypoglycemia has been associated, in at least one instance, with an inflammatory pseudotumor of the pancreas graft.²⁸

Sixth, severe hypoglycemia was observed in one recipient who had developed nesidiodyplasia of the pancreas graft.²⁹

Fortunately, the vast majority of hypoglycemic episodes are clinically benign and self-limiting. The reason may be that symptom responses to hypoglycemia are fully restored in recipients of functioning pancreas grafts.²³ If symptoms persist, the diagnosis of hypoglycemia must first be confirmed by means other than a home glucometer (which can deliver falsely low results): Glucose measurements must be assessed by a regular laboratory. For most pancreas recipients with confirmed hypoglycemic episodes, dietary modification (e.g., increased intake of complex carbohydrates, increased meal frequency) should suffice. Only under exceptional circumstances should diazoxide, somatostatin, glucagon, or transplant pancreatectomy be necessary.^{21,29,30}

References

1. International Islet Transplant Registry Newsletter 9. 2001;8.
2. Ramcharan T, Paraskevas S, Denis R, et al. Primary nonfunction after pancreas transplant—an uncommon cause of graft failure. *Acta Chir Austriaca* 2001;33(suppl 174):12.
3. Wadström J, Gannedahl G, Wahlberg J, et al. Development of type II diabetes after combined kidney-pancreas transplantation in a patient with type I (insulin-dependent) diabetes. *Transplant Proc* 1994;26:1761–1762.
4. Troppmann C, Gruessner AC, Benedetti E, et al. Vascular graft thrombosis after pancreatic transplantation: Univariate and multivariate operative and nonoperative risk factor analysis. *J Am Coll Surg* 1996;182:285–316.
5. Weide LG, Stratta RJ, Cushing K, et al. Elevated fasting pro-insulin levels as a marker for impaired function after pancreas transplantation. *Transplant Proc* 1997;29:678.
6. Büsing M, Hopt UT, Quacken M, et al. Morphological studies of graft pancreatitis following pancreas transplantation. *Br J Surg* 1993;80:1170–1173.
7. Nghiem DD, Hsia S, Schlosser JD, Nghiem HG. Delayed endocrine graft function: Truth or myth? *Transplant Proc* 1998;30:284.
8. Troppmann C, Gruessner AC, Papalois BE, et al. Delayed endocrine pancreas graft function after simultaneous pancreas-kidney transplantation. *Transplantation* 1996;61:1323–1330.
9. Troppmann C, Gillingham KJ, Benedetti E, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. *Transplantation* 1995;59:962–968.
10. Jones JW Jr, Mizrahi SS, Bentley FR. Type II diabetes after combined kidney and pancreas transplantation for type I diabetes mellitus and end-stage renal disease. *Clin Transplant* 1996;10:574–575.
11. Smith JL, Hunsicker LG, Yuh WTC, et al. Appearance of type II diabetes mellitus in type I diabetic recipients of pancreas allografts. *Transplantation* 1989;47:304–311.
12. Larsen JL, Stratta RJ, Miller SA, et al. Evidence that fasting hyperproinsulinemia after combined pancreas-kidney transplantation diminishes over time. *Transplantation* 1993;56:1533–1537.
13. Andersen HB, Christiansen E, Burchard F, et al. Remission of pancreatic graft failure by intensive insulin treatment. *Clin Transplant* 1990;4:251–253.
14. Barone GW, Henry ML, Elkhannas EA, et al. Pancreatic exocrine “burnout” following pancreas transplantation. *Transplant Proc* 1992;24:831–832.
15. Redmon JB, Teuscher AU, Robertson RP. Hypoglycemia after pancreas transplantation. *Diabetes Care* 1998;21:1944–1950.
16. Larsen JL, Stratta RJ, Miller SA, Taylor RJ. Hypoglycemic symptoms following pancreas transplantation. *Clin Transplant* 1993;7:520–524.
17. Cottrell DA, Henry ML, O’Dorisio T, et al. Hypoglycemia after successful pancreas transplantation in type I diabetic patients. *Diabetes Care* 1991;14:1111–1113.
18. Zehrer CL, Gross CR. Prevalence of “low blood glucose” symptoms and quality of life in pancreas transplant recipients. *Clin Transplant* 1993;7:312–319.
19. Battezzati A, Bonfatti D, Benedini S, et al. Spontaneous hypoglycemia after pancreas transplantation in type I diabetes mellitus. *Diabetic Med* 1998;15:991–996.
20. Tran MP, Larsen JL, Duckworth WC, et al. Anti-insulin antibodies are a cause of hypoglycemia following pancreas transplantation. *Diabetes Care* 1994;17:988–993.
21. Hirshberg B, Trelezky V, Raz I. Hypoglycaemia following pancreatic allograft transplantation. *J Intern Med* 1998;243:389–393.
22. Diem P, Abid M, Redmon JB, et al. Systemic venous drainage of pancreas allografts as independent cause of hyperinsulinemia in type I diabetic recipients. *Diabetes* 1990;39:534–540.
23. Kendall DM, Rooney DP, Smets YFC, et al. Pancreas transplantation restores epinephrine response and symptom recognition during hypoglycemia in patients with long-standing type I diabetes and autonomic neuropathy. *Diabetes* 1997;46:249–257.
24. Battezzati A, Luzi L, Perseghin G, et al. Persistence of counter-regulatory abnormalities in insulin-dependent diabetes mellitus after pancreas transplantation. *Eur J Clin Invest* 1994;24:751–758.
25. Diem P, Redmon JB, Abid M, et al. Glucagon, catecholamine and pancreatic polypeptide secretion in type I diabetic recipients of pancreas allografts. *J Clin Invest* 1990;86:2008–2013.
26. Redmon JB, Kubo SH, Robertson RP. Glucose, insulin, and glucagon levels during exercise in pancreas transplant recipients. *Diabetes Care* 1995;18:457–462.
27. Barrou Z, Seaquist ER, Robertson RP. Pancreas transplantation in diabetic humans normalizes hepatic glucose production during hypoglycemia. *Diabetes* 1994;43:661–666.
28. Remberger K, Weiss M, Gokel JM, et al. Pancreatic inflammatory pseudotumor with persistent hyperinsulinemia and hypoglycemia following long term pancreatic transplantation. *Verh Dtsch Ges Path* 1987;71:328–332.
29. Semakula C, Pambuccian S, Gruessner R, et al. Clinical case seminar: Hypoglycemia after pancreas transplantation: Association with allograft nesidiodyplasia and expression of islet neogenesis-associated polypeptide. *J Clin Endocrinol Metab* 2002;87:3548–3554.
30. Osei K. Post-transplantation hypoglycemia in type I diabetic pancreas allograft recipients. *Acta Diabetol* 1998;35:176–182.

9.2.5

Posttransplant Malignancies

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De novo malignancies, a proven and undeniable risk for chronically immunosuppressed solid-organ transplant recipients, are seen with increasing frequency now that outcomes have improved and patient survival routinely extends into decades. The malignancies posing the most significantly increased risk for recipients treated with cyclosporin A have been outlined by Penn and Brunson¹: skin cancers, Hodgkin's lymphoma, and Kaposi's sarcoma. Other histologic types, more common in the general population, pose no increased risk for transplant recipients. Certain malignancies, notably posttransplant lymphoproliferative disorder (PTLD), are peculiar to solid-organ transplant recipients. The known risk factors include viral infection—such as Epstein-Barr virus (EBV), human papilloma virus (HPV), and cytomegalovirus (CMV)—in combination with immunosuppression, including antilymphocyte preparations.

PTLD

PTLD, a spectrum of diseases of the lymphoid cell lineage, often affects solid-organ transplant recipients. It is variously categorized by histopathologic, molecular, and clinical characteristics. The incidence in transplant recipients ranges from 0.8% to 20%. The precise incidence, diagnosis, and treatment rely extensively on the method of classification. EBV, a member of the herpes virus family, has been implicated in the pathogenesis of Burkitt's lymphoma, carcinoma of the nasopharynx, and Hodgkin's disease. In immunosuppressed transplant recipients, EBV infection plays a crucial role in the development of PTLD.² After primary EBV infection from an EBV-positive donor to an EBV-negative recipient, the most common risk factors for the development of PTLD are the use of antilymphocyte antibody preparations and concur-

rent CMV.³ EBV-driven B-cell proliferation spans a wide range of clinical and pathologic manifestations, from more benign and reversible polyclonal proliferation to malignant lymphomas.

Two strains of EBV are known, together accounting for an almost ubiquitous exposure in the general population. In Western industrialized countries, the incidence of EBV immunity reaches 90% by age 40.⁴ EBV-1 and EBV-2 differ in their expression of genes encoding the nuclear antigens designated as EBNA-2, -3A, -3B, and -3C. They also differ in their geographic distribution, with EBV-1 being more common in the Western hemisphere and EBV-2 found in Africa and New Guinea.⁵ In immunocompetent individuals, EBV infection is held in check by cytotoxic T cells and perhaps by natural killer (NK) cells as well.⁶ Humoral immunity has also been documented.⁷

EBV Infection and Pathogenesis of B-Cell Transformation

Transmission of EBV from a seropositive donor to a naïve recipient is virtually 100%.⁸ Infection of B cells with EBV begins with the binding of outer envelope glycoproteins with the cell surface marker CD21. Infected B cells express adhesion molecules, B-cell activation markers, and latent viral proteins.⁹ Latent infection, without the replication or release of virus particles, results in the expression of 11 viral genes: 6 nuclear proteins called EBNA; 3 integral membrane proteins, LMP-1, -2A, and -2B; and 2 small EBV-encoded non-polyadenylated RNAs, EBER-1 and EBER-2.¹⁰ The latter two are also highly expressed and are useful in identifying infected cells. The linear EBV genome circularizes to form an episome, resulting in the transformation of B cells and their autonomous growth.

Normally, cells expressing EBV antigens are eliminated by cytotoxic T lymphocytes (CTLs); CD8⁺ CTLs directed against viral markers are seen in high numbers in seropositive, healthy individuals.¹¹ Several mechanisms are used by the EBV-infected B cell to evade the immune response. Infected B cells fail to express B7, a molecule required for co-stimulatory T-cell activation. In addition, some forms of latent infection result in the expression of a single viral gene, EBNA-1. This gene includes a promoter sequence protecting it from the HLA class I antigen processing pathway and is thus unavailable for presentation to CD8⁺ CTLs. After a solid-organ transplant, the CTL response is blunted further by the administration of antilymphocyte preparations, which can result in the release of cytokines known to favor B-cell growth (such as interleukin-6 [IL-6]) and cytokines inhibiting the T-cell response (such as IL-10).¹² The degree of viral load has been thought to correlate with primary infection and with the development of PTLD in solid-organ transplant recipients.^{13,14} Antibody levels correlate poorly with infection, but transplant recipients, in particular those who develop PTLD, have low or absent levels of anti-EBNA antibodies.

Transformation of B cells gives rise initially to polyclonal expansion. Differential sensitivity to host CTLs may result in oligoclonal or monoclonal characteristics in the lesion as certain clones gain a growth advantage. Cytogenetic abnormalities are accumulated, in particular those involving proto-oncogenes or mutations in tumor suppressor genes. Frank neoplastic transformation ensues, resulting in a monoclonal malignancy.¹⁵

Classification

After their first description in solid-organ transplant recipients in 1968,¹⁶ the recognition slowly grew that these PTLD lesions were lymphoid tumors capable of regression. The first PTLD classification system, proposed by Frizzera et al. in 1981, relied purely on histologic criteria,¹⁷ as did subsequent modifications, as well as a new schema proposed by Nalesnik et al.¹⁸ The first classification system using genotypic data was introduced in 1989 by Locker and Nalesnik.¹⁹ This system was the first to recognize the importance of EBV DNA incorporation and the clonality of the infected cells. But it is now obsolete, given the recognition of other forms of PTLD, such as T-cell PTLD and EBV-negative PTLD. A still more comprehensive classification system was introduced in 1995 at the Workshop of the Society of Hematopathology.²⁰ This system recognizes three basic categories of PTLD: benign lesions, B-cell PTLD, and T-cell PTLD. The B-cell category is further divided into (1) plasmacytic hyperplasia, (2) polymorphic PTLD, and (3) malignant lymphoma and multiple myeloma (Fig 9.2.5.1).

Plasmacytic Hyperplasia

Histologically, lesions in this subcategory show preservation of the normal lymph node architecture, with small, minimally

atypical lymphoid cells proliferating in the interfollicular area. This subcategory includes lesions that are polyclonal and do not usually express immunoglobulin (Ig) gene rearrangements. Similarly, mutations to proto-oncogenes or tumor suppressor genes are rare in this subcategory. Evidence of EBV infection is common and can be either monoclonal or polyclonal. In general, the prognosis for these lesions is good: Recurrence is rare.

Polymorphic PTLD

This is the most common subcategory of PTLDs. These lesions show obliteration of normal histologic architecture by a polymorphic cell population; some areas have a monotonous cellular appearance. Also, some areas of necrosis are common. At the molecular level, Ig gene rearrangements are common, but proto-oncogene alterations are not. Clonal EBV infection is seen in most cases. These lesions classically appear within 1 to 2 years posttransplant as stage I, II, or, III disease. Multi-agent chemotherapy is the treatment of choice if the lesions do not regress with a reduction in immunosuppression.

Malignant Lymphoma and Multiple Myeloma

In this subcategory, lesions are clinically and histologically similar to the malignant lymphoma seen in immunocompetent individuals. Lesions are largely diffuse, large-cell lymphomas or multiple myelomas. Histologically, they appear as monotonous cell populations destroying the normal architecture of the tissues in which they appear. Extranodal sites are frequently involved, including the central nervous system, abdominal viscera, and solid-organ allograft. Multiple myeloma lesions contain malignant-appearing plasma cells. Most of these lesions demonstrate B-cell phenotypic markers and have clonal rearrangements of Ig heavy and light chains. They also consistently express structural alterations of proto-oncogenes or tumor suppressor genes. These lesions typically have a more aggressive clinical course: They are more advanced at presentation and less responsive to multiagent chemotherapy.

T-Cell PTLD

T-cell lesions are a rare variety of PTLD, with a small number of cases reported.^{21–24} They usually occur much later (median, 5 years posttransplant) than the B-cell variety (median, <1 year). Allograft involvement is rare with T-cell lesions, in contrast to B-cell lesions. EBV-positive cases, accounting for <50% of T-cell PTLD, tend to occur later than non-EBV-associated PTLD. EBV infection of T cells may be mediated by the CD21 receptor.²⁵ Clinically, T-cell PTLD lesions tend to behave more aggressively than the three more common types mentioned above.

Clinical Presentation

The most common manifestation of PTLD is viral illness with fever, pharyngitis, myalgia, and lymphadenopathy, usually

FIGURE 9.2.5.1. (A) PTLD: hyperplastic type with expansion of the B- and T-cell regions with architectural maintenance (CD3 immunostain with darker T-cell regions and pale B-cell follicles). (B) PTLD: polymorphic type with a heterogeneous spectrum of small and large cells (hematoxylin and eosin stain). (C) Monomorphic posttransplant lymphoma: diffuse, large-cell type, B-cell phenotype with intermixed nonneoplastic small T cells (hematoxylin and eosin stain).

A

B

C

within the first year posttransplant. Localized adenopathy may on occasion be seen, but widespread disease is more common at the time of presentation. Other clinical aspects depend on the organ system involved. Primary allograft involvement as the presenting feature is seen in roughly 17% of kidney allograft recipients with PTLT, 9% of liver recipients, and 60% to 80% of lung and intestinal allograft recipients with PTLT. Allograft involvement as a whole is common in kidney recipients. Heart allograft involvement is rare.

Because PTLT may present with allograft dysfunction in the first few months posttransplant, the diagnostic challenge is to differentiate it from acute rejection: The respective treatments are at opposite ends of the therapeutic spectrum.^{26,27} In the pancreas, one study recently found that with acute rejection were inflammatory infiltrates composed of mixed small and large activated T cells, with a minority of other cell types (usually eosinophils and neutrophils). The areas of involvement typically included acini; acinar cell damage was the hallmark. Arterial wall involvement was common (manifesting as endotheliitis), as was ductal inflammation. In biopsy specimens positive for PTLT, the infiltrates consisted of a substantial proportion of atypical B cells. They involved the pancreatic parenchyma randomly, without affinity for the acini, were often nodular, and involved peripancreatic tissue. Arterial walls were spared, although venous endotheliitis was seen. Other studies have found other markers to be useful in distinguishing PTLT from acute rejection, such as in situ hybridization for EBV.²⁸

Radiologically, PTLT in the pancreas may present as non-specific or diffuse allograft enlargement, as reported by Meador et al.²⁹ The differential diagnosis for this finding includes graft pancreatitis or rejection—conditions that may be excluded only by biopsy results or by the presence of extra- or intra-allograft focal masses.

Treatment

Reduced Immunosuppression

The first and most essential step in PTLT treatment is to reduce immunosuppression. Starzl et al. first described this approach in the early 1980s.³⁰ Most centers still report regression of poly- and monoclonal EBV-associated lesions in 23% to 86% of patients whose primary or only therapy is reduction of immunosuppression.³¹ Such a great variation in effectiveness may be due to the array of definitions of PTLT and the inclusion, in some reports, of lesions that would otherwise be considered to represent benign hyperplasia. Still, a substantial number of recipients will respond to reduced immunosuppression alone, usually within 2 to 4 weeks. The goal of this approach is to allow re-establishment of the population of CTLs capable of attacking EBV-infected cells. Interestingly, solid-organ rejection has rarely been reported in this context, a testament to the deep state of immunosuppression exhibited by these recipients. In our series at the University of Minnesota, none of the

pancreas recipients experienced rejection as a result of reduced immunosuppression. For pancreas recipients, as for kidney and liver recipients, it is sufficient to stop calcineurin inhibitors, azathioprine, and/or mycophenolate mofetil and only continue prednisone at maintenance levels. However, for heart, lung, and intestinal recipients maintenance of low levels of calcineurin inhibitors is recommended because of the greater risk and sequelae of rejection.³¹

In a recent study of 42 adult solid-organ transplant recipients who developed PTLT and whose treatment involved reduced immunosuppression, Tsai et al. identified some prognostic factors associated with failure of this approach. Of 30 recipients treated with reduced immunosuppression alone, 19 (63%) experienced complete remission of their PTLT (median time, 3.6 weeks). Multivariate analysis showed that an elevated lactate dehydrogenase ratio, organ dysfunction, and multiorgan PTLT involvement were independent prognostic factors associated with lack of response to reduced immunosuppression. Of those 30 recipients, recipients with none of these prognostic factors had a response rate of 89% (16/18); with one prognostic factor, 60% (3/5); and with two or three prognostic factors, 0% (0/7).³² Univariate analysis showed that low-grade PTLT also contributed to favorable response but did not contribute independent information when other factors were considered. Other studies have also examined prognostic factors, albeit less thoroughly. In one study, the incidence of allograft rejection was about 39%; these rejection episodes were easily treated, with only one case of graft loss.^{33,34}

Cytotoxic Chemotherapy

The need for chemotherapy appears to be increased in adult pancreas recipients and in those of any age who develop PTLT more than 2 years posttransplant; both of these subgroups are less likely to respond to a reduction of immunosuppression. Some authors have suggested that identifying molecular markers (such as oncogene expression or tumor suppressor gene mutation) may offer a chance to identify, at the time of PTLT diagnosis, those recipients likely to require and respond to cytotoxic chemotherapy. The agents used vary from center to center, but most centers closely duplicate their protocols for true malignant lymphomas. Routine use of chemotherapy is controversial and is usually reserved for monomorphic, aggressive lesions appearing late after transplantation.

Antibody Therapy

An anti-CD20 chimeric human–murine monoclonal antibody, rituximab, is potentially useful for treating CD20-positive B-cell lesions. CD20 is not normally expressed on hematopoietic stem cells or other cell types. Anecdotal reports have been published on the efficacy of this antibody in PTLT in general^{35,36} and in pancreas transplantation in particular.³⁷ In a study by Milpied et al.,³⁸ 26 of 32 patients treated with this antibody

were solid-organ transplant recipients, including 1 kidney–pancreas recipient. In most cases, the antibody was used as primary therapy in conjunction with reduced immunosuppression. The response among the solid-organ recipients was 65%, including two partial responses. The projected 1-year survival of the responders was 73%. More recent case reports have suggested a role for rituximab in conjunction with the antiviral cidofovir, in the treatment of PTLT with central nervous system (CNS) involvement.³⁹ To date, no multicenter randomized controlled clinical trials reported on the efficacy of this antibody. But it remains promising, both as first line and as salvage therapy, with few reported side effects. The utility of rituximab in treating non-CD20-expressing lesions is unknown.

Antiviral Agents

The theoretical advantage of antiviral therapy lies in its potential prevention, rather than treatment, of EBV-induced PTLT. Both acyclovir and ganciclovir effectively inhibit EBV genome replication *in vitro*.⁴⁰ These agents help suppress the lytic phase of EBV replication, but their effect on the latent phase, in which proliferation of transformed B cells occurs, is limited.³ Nonetheless, and despite limited evidence-based support, antivirals remain a routine component of PTLT treatment regimens.

However, if the lytic phase accounts for much of the viral replication *preceding* clinical PTLT, then there would be a role for antivirals in PTLT prevention as well.^{41–43} Measurement of the EBV viral load by quantitative polymerase chain reaction (PCR) assays showed a 30- to 40-fold increase in this parameter in transplant patients with PTLT, as compared with those with normal latency.^{44–46} Kenagy et al. estimated that the EBV viral load rises 1 to 4 months before diagnosis of PTLT,⁴⁴ an estimate that other studies have supported.^{45,47} Davis et al. ascribed the lower than expected incidence of PTLT in EBV-seronegative recipients of a seropositive organ as due, in part, to the preventive effects of ganciclovir⁴⁸; they suggested that while EBV infection may not be prevented, it may be contained to a point that is manageable for the immunosuppressed host. Green et al. developed a protocol for EBV viral load monitoring using preemptive ganciclovir and CMV immune globulin; the incidence of PTLT in their pediatric intestinal transplant recipients dropped from 40% to 11%.^{49,50} The association of CMV infection with subsequent PTLT has been noted, although a mechanism by which CMV might assist B-cell transformation has not been identified.⁵¹ The effect of antivirals on the development of PTLT may be mediated by their effect on CMV or by a direct effect on lytic EBV replication.

Surgery

Surgical resection of PTLT lesions is useful in certain circumstances, usually if gastrointestinal involvement is isolated, with or without perforation, and if local growth compresses or compromises vital structures. If PTLT is disseminated, the

role and effectiveness of surgical therapy is largely limited to the control of acute symptoms.¹⁸

Radiation

Radiation therapy remains the primary and most effective treatment for PTLT in the context of CNS disease. It has been of limited value in the control of lesions elsewhere.

Interferon- α

Limited clinical experience suggests a potential role for interferon- α (IFN- α)-based regimens in the treatment of PTLT. Davis extensively reviewed the use of interferon in PTLT.⁵² Its potential mechanisms include inhibition of viral replication, tumoricidal activity that may include increased expression of Fas ligand, increased cytotoxicity of NK cells, and enhanced HLA expression that may increase T-cell cytotoxicity. No randomized trials have been performed, but the most extensive experience suggests a response rate approaching 40% to 50%.⁵³ In that study by Davis et al., acute rejection precipitated by IFN therapy was reported in about 30% of solid-organ recipients; it was easily treated with steroids and cessation of IFN therapy. Rejection was also considered a marker of restored immune system function, although long-term follow-up showed complete responses to be rare.

Passive Immunotherapy

Intravenous Ig (IVIg) has been used as an adjunct to IFN- α in a number of case reports.^{54–56} Its use stems from the recognition that PTLT is associated with decreased or absent levels of antibodies against EBNA^{45,57} and that increasing levels of antibodies are associated with a decline in EBV viral load.⁴⁵

Anecdotal reports have described some success with adoptive immunotherapy using EBV-specific, partially HLA-matched CTLs of unrelated donor origin⁵⁸ or using autologous CTLs isolated and expanded *in vitro*.⁵⁹ Other authors using IL-2-lymphocyte activated killer (LAK) cells derived from pancreas recipients have reported marked, long-standing regression of PTLT lesions.⁶⁰ All these approaches are, in essence, an attempt to restore the specific immunologic defect that allowed PTLT to develop initially. The particular difficulties faced in treating solid-organ recipients with EBV-specific CTLs include isolating and expanding recipient cells or inducing them to function in immunosuppressed individuals without compromising the graft. The efficacy of these protocols is variable, and although promising, they have yet to be evaluated in formal trials.

PTLT in Pancreas Transplantation: Reported Experience

Few reports focus on PTLT after pancreas transplants, in contrast to the extensive published series on liver, kidney, and

thoracic transplants. Most reported cases of PTLD are mentioned in larger multiorgan series, which rarely include more than one or two pancreas recipients (Table 9.2.5.1). Keay et al. described four cases of early onset PTLD, each presenting within 62 days after a pancreas transplant.⁶¹ The use of OKT3 for induction immunosuppression was associated with PTLD; the use of Thymoglobulin was not. The absence of antiviral prophylaxis was significantly associated with PTLD; seroconversion for CMV was not. Treatment varied with the severity of PTLD, but included reduced immunosuppression and pancreas allograft removal in all four cases. In the two cases of intermediate severity (polymorphic PTLD), IFN- α and IVIg were added to high-dose antiviral therapy; in the most severe case (monomorphic PTLD and malignant lymphoma), chemotherapy was given. All four recipients had a favorable course and remained PTLD-free for at least 1.5 years after treatment.

Kroes et al. reported PTLD in a simultaneous pancreas-kidney recipient.⁶² Diagnosed 15 days posttransplant, it manifested as generalized lymphadenopathy; computed tomography revealed an edematous pancreas graft and multiple perfusion defects in the kidney graft. Given its acuity and early onset, immunosuppression was stopped, both grafts were removed, and the recipient was treated with anti-CD19 monoclonal antibody, γ -globulin, acyclovir, and IFN- α . The recipient had been seronegative several months pretransplant but apparently contracted EBV recently pretransplant from her companion, as suggested by PCR and Western blot analysis of EBNA1 and 6. Primary infection by EBV has, in general, been assumed to occur via the donated organ. This case showed that additional risk exists for recipients who undergo induction immunosuppression during a period of primary infection with a coincident phase of B-cell proliferation.

PTLD in Pancreas Transplantation: The University of Minnesota Experience

From January 1989 through December 2001, 1,172 patients underwent pancreas transplants at the University of Minnesota: 235 pancreas transplant alone (PTA) recipients; 422 pancreas after kidney (PAK) recipients; and 515 simultaneous pancreas and kidney (SPK) recipients. In that time span, we diagnosed 15 recipients with PTLD. The lesions covered the spectrum from polymorphic disease to malignant B- and T-cell lymphomas. Recipient and tumor characteristics are outlined in Table 9.2.5.2.

At the time of their first transplant, recipients ranged in age from 27 to 48 years (mean, 41 ± 2). For those with the B-cell lineage lymphomas, the mean time to PTLD diagnosis in pancreas (SPK, PAK, and PTA) recipients was 1.5 ± 0.5 years, which compared unfavorably to kidney transplant alone (KTA) recipients (5.2 ± 1.2 years) and liver recipients (3.8 ± 1.6 years). The difference was not significant, but a shorter latency period for all pancreas recipients was suggested ($P = 0.07$). Recipients with T-cell lesions exhibited a wide range of latency periods: 6.7 ± 2.8 years for pancreas (SPK, PAK, and PTA) recipients vs 16.6 ± 3.2 years ($P = 0.04$) for kidney (KTA) recipients. No T-cell lesions were seen in liver or small-bowel recipients.

Over time, the latency period has decreased in the more recent immunosuppressive era (1994 through 2001) vs the earlier era (1989 through 1994) (2.4 ± 0.9 vs 5.5 ± 3.5 years). This finding may suggest a progression toward more aggressive disease as immunosuppression becomes more potent. Libertiny et al. made similar observations in kidney recipients.⁶³ They documented an increase in the incidence of PTLD, which was primarily due to an increase in early lesions. In our ex-

TABLE 9.2.5.1. Reported cases of PTLD in pancreas (PAK, PTA) and pancreas/kidney (SPK) recipients.

Series	No. of patients reported	Cell type	Histologic findings	Treatment*
Walker et al. ⁶⁴	4	B	2 polymorphic, 2 monomorphic	Antivirals, chemo
Kroes et al. ⁶²	1	B	Polymorphic	Graft removal, antivirals, anti-CD19, IVIg, IFN- α
Martinenghi et al. ⁸⁶	2	B	Monomorphic	
Keay et al. ⁶¹	4	B	1 plasmacytic hyperplasia, 2 polymorphic, 1 monomorphic	Graft removal, antivirals, IVIg, IFN- α , chemo
Drachenberg et al. ²⁸	4	B	3 polymorphic, 1 monomorphic, immunoblastic lymphoma	Graft removal, chemo for monomorphic disease
Davis, ⁵² Davis et al. ⁵³	3	B	—	Rituximab, IVIg, IFN- α , chemo
O'Dwyer et al. ³⁷	1	B	—	Rituximab
Milpied et al. ³⁸	1	B	—	Rituximab
Tsai et al. ³²	4	B	—	Antivirals, chemo in 3/4
Egidi ⁸⁸	5	4 B 1 T	—	2 graft pancreatectomy, 1 graft nephrectomy, 4 antivirals and IVIg; 1 chemo and RTX

*Treatment included reduced immunosuppression in all cases. RTX, radiation therapy; chemo, chemotherapy.

TABLE 9.2.5.2. PTLD in pancreas recipients at the University of Minnesota, 1989–2001: Recipient and tumor characteristics.

Patient no.	Tx type	Sex	Age at Tx	CMV D/R status	Pretx EBV status	PTLD onset (mo post Tx)	Cell type	EBV	CD20	Diagnosis	Clonality	Extranodal involvement sites	Treatment	Follow-up (mos)	Patient status on Dec 31, 2001
1	SPK	M	40	NA/–	NA	NA	T	NA	Neg	Unknown	Unknown	Skin	Surgery	NA	Dead
2	SPK	M	35	NA/NA	NA	2	B	Pos	Pos	DLCL	IgM- κ	Liver, kidney	Chemo	1	Dead
3	SPK	M	34	+/+	Neg	68	T	Neg	Neg	Anaplastic	T-cell β	Liver, spine, bone marrow	Chemo, RTX, surgery	20	Dead
4	SPK	M	43	NA/NA	NA	7	B	Pos	Neg	Myeloma	IgA- λ	Kidneys, heart, bone marrow, kidney or pancreas graft	None	<1	Dead
5	SPK	M	44	+/+	NA	43	B	NA	Pos	DLCL	NA	Liver	Chemo	37	Alive
6	SPK	F	48	NA/–	Neg	5	B	Pos	Pos	DLCL	NA	Stomach, intestine	None	<1	Dead
7	PTA	M	38	–/–	Neg	7	B	Pos	Pos	DLCL	IgG- κ	Stomach, intestine, colon	Chemo, surgery	<1	Dead
8	SPK	M	43	NA/+	Pos	35	B	Neg	Pos	DLCL	Positive IgG (PCR)	CNS, liver, spleen, bone marrow	Chemo, RTX	13	Dead
9	SPK	M	45	–/–	Pos	55	B	Neg	Neg	DLCL	NA	Stomach, mesentery	Unknown	5	Alive
10	PAK	M	46	–/+	Pos	13	B	Pos	Pos	DLCL	NA	CNS	RTX	2	Dead
11	PAK	M	46	NA/NA	NA	132	T	Pos	Neg	DLCL	NA	CNS	RTX	22	Dead
12	SPK	M	38	+/+	Pos	4	T	ND	Neg	Peripheral T, mixed	NA	Soft tissues	None	2	Alive
13	SPK	F	36	–/NA	NA	7	B	Pos	Pos	DLCL	IgG- κ	Lung, colon, vallicula	Anti-CD20	1	Dead
14	PAK/PAK	M	41	–/–	Pos	19	T	Pos	Neg	Peripheral T, mixed	T-cell β and γ	Graft kidney	Chemo	4	Alive
15	PTA	M	27	–/–	Neg	4	B	Pos	Pos	DLCL	NA	Bone marrow	Chemo	1	Alive

Tx, transplant; NA, not available; DLCL, diffuse large-cell lymphoma; RTX, radiation therapy; Pos, positive; Neg, negative; chemo, chemotherapy; D, donor; R, recipient.

perience, the increasing incidence of early lesions cannot be ascribed to the increased use of antilymphocyte preparations, one of the known risk factors for PTLT. An examination of the 15 University of Minnesota cases showed that the use of antilymphocyte preparations such as Minnesota antilymphocyte globulin (MALG), antithymocyte globulin (ATG), and OKT3 decreased over time. In era 1 recipients who developed PTLT were exposed to a mean of 25 ± 5 doses each and in era 2 to a significantly lower 10 ± 0.8 doses each ($P < 0.05$).

Organ-specific differences were also seen with respect to patient survival ($P = 0.07$) (Fig 9.2.5.2). In pancreas recipients, PTLT appears to carry a more severe prognosis. The 50% cumulative survival time was 0.16 years in pancreas recipients, in contrast to 1.7 years for kidney recipients. With follow-up periods of up to 9 years, 57% of liver or small bowel recipients were still living at the end of 2001. The 50% cumulative survival times, stratified for B- and T-cell lesions, are shown in Table 9.2.5.3. Of interest, pancreas recipients had shorter survival times with B-cell lesions than kidney recipients but longer survival times than the kidney recipients with T-cell lesions. Because of the small numbers involved, these recipients are asymmetrically distributed in time, with the pancreas recipients being much more recent. Improved chemotherapy or more aggressive treatment may account for the difference in survival. B-cell lesions are in general associated with greater long-term survival, but no significant difference was seen between pancreas recipients with B- vs T-cell lesions (Cox–Mantel test) (Fig 9.2.5.3). Similarly, no difference was seen between pancreas recipients with EBER- vs EBER+ lesions.

To evaluate the effect of the latency period on prognosis, the 15 recipients with PTLT were stratified by length of the latency period; Kaplan–Meier survival curves were compared using the Cox–Mantel test. Two analyses were conducted, using 1 year posttransplant, then 3 years, as the defining limit of early onset. Both analyses showed a significant difference

TABLE 9.2.5.3. Organ-specific survival for recipients with PTLT, University of Minnesota, 1988–2001

Cell type	50% Cumulative survival time (y)		
	Pancreas	Kidney	Liver/small bowel
B	0.09	3.7	>9
T	1.2	0.14	N/A

in survival rate: The early onset lesions in all cases were associated with a significantly decreased survival time (Fig 9.2.5.4). Other published series have described a similar trend in mortality with early onset PTLT.⁶⁴

Widespread involvement was common in the 15 recipients, with most lesions involving extranodal sites at the time of presentation. Several cases involved bone marrow at the time of diagnosis; the incidence was close to 50% in the 10 recipients with B-cell lesions (vs only 6% of kidney recipients with PTLT and none of the liver recipients with PTLT in the University of Minnesota series [$P = 0.05$]). In pancreas recipients, the mean number of organs involved at diagnosis was 3.7 ± 2.0 . This number was significantly greater than in liver or small-bowel recipients (2.0 ± 1.5) or in kidney recipients (1.7 ± 1.2) ($P = 0.007$). Gastrointestinal involvement was seen in 4 of the 15 pancreas cases, with liver involvement appearing in 3 more; it was associated with a diminished survival rate and a more fulminant clinical course, whether or not gastrointestinal morbidity was observed. Central nervous system involvement was not associated with a high mortality rate; survival in such recipients exceeded 12 months.

Perhaps the most salient characteristic of the 15 recipients with PTLT was the relatively high proportion of T-cell lesions. Although rare in other graft types, the incidence of T-cell PTLT in the University of Minnesota series was 33%. In two recipients, EBV+ T-cell PTLT was documented. This is a rare variant, with only 16 cases reported in the literature.²⁵

FIGURE 9.2.5.2. Kaplan–Meier survival curves for all solid-organ transplant recipients with PTLT at the University of Minnesota, 1989–2001, grouped by type of organ transplant. Data points indicate censor times. Differences between the three groups approached significance ($P = 0.07$). Pancreas (PAK, PTA) or pancreas–kidney (SPK) transplant recipients had a markedly lower survival than either kidney recipients or liver or small-bowel recipients.

FIGURE 9.2.5.3. Kaplan–Meier survival curve for pancreas recipients with PTLD at the University of Minnesota, 1989–2001, grouped by cell type. Data points indicate censor times. There was no significant difference between the two groups ($P = 0.19$).

FIGURE 9.2.5.4. Kaplan–Meier survival curve for pancreas recipients with PTLD at the University of Minnesota, 1989–2001, grouped by disease latency. Data points indicate censor times. (A) Onset of disease within 1 year posttransplant was defined as early; the difference in survival between early and late was significant ($P = 0.015$). (B) Early onset was defined as within 3 years; Again, the difference between groups was significant ($P = 0.001$).

The University of Minnesota series excluded plasmacytic hyperplasia, focusing only on mono- and polymorphic PTLD and on malignant lymphoma. These entities represent a continuum of disease, so false elevation of incidence or longer survival times may result from the inclusion of more benign lesions. Clearly, a strict standardized approach to diagnosis and reporting of these cases is mandated, so that meaningful interpretation of treatment protocols can be made.

Solid Tumors

Solid tumors occurring after pancreas transplants include (1) those involving the graft, (2) those involving the urinary tract, and (3) systemic tumors.

Graft-Related Tumors

Graft-derived tumors remain more a theoretical than a real risk to pancreas recipients. The organ commonly associated with the development of primary tumors posttransplant is the liver; anecdotal reports of renal cell carcinoma after kidney transplants have also been published.^{65,66} A single case of pancreatic adenocarcinoma was reported in an SPK recipient, a 45-year-old male who received both grafts from a 55-year-old male donor.⁶⁷ At 3.5 years posttransplant, the recipient had an ileal perforation; the excised bowel showed moderately differentiated adenocarcinoma of pancreatic origin. The explanted pancreas was diffusely infiltrated with tumor; after DNA sequencing, the tumor was identified as of donor origin. Despite cessation of all immunosuppression and treatment with cisplatin, IL-2, and interferon, the cancer progressed and the recipient died 11 months after diagnosis. With continuing efforts to expand the cadaver organ pool and the resulting increase in donor age limits, careful attention to organ-specific risk factors and proper assessment of the pancreas at procurement are ever more important. In this reported case, the pancreas was normal at procurement but the donor's age was a risk factor for harboring occult tumor.⁶⁸

In the transplanted pancreas, no reported cases of insulinoma or other endocrine cell tumors have been reported. Hypoglycemia is a relatively frequent consequence of a pancreas transplant, occurring in up to 50% of recipients,^{69–71} but no cases have been definitively linked to pancreatic microadenomas. Proliferative stimuli may be exerted on islets by chronic metabolic stress, as illustrated in an animal model of transplanted β -cell transformation.⁷² Semakula et al. reported nesidioblastosis in a pancreas allograft that was associated with hypoglycemia.⁷³ In their study of a recipient with severe posttransplant hypoglycemia, the explanted pancreas showed small islets budding off ductules; intralobular islet cell aggregates; and large, hyperchromatic islet cell nuclei, or "nesidioblastosis." These proliferating islet lesions and associated ductal cells stained positive for the islet neogenesis associated protein (INGAP).⁷⁴

Another site of potential risk is the duodenum of the bladder-drained pancreas (see chapter 8.2.2). The primary evidence of such a risk is the reported incidence of tumors in ileal conduits and bladder augmentations, where the transforming agent has been the chronic exposure of intestinal epithelium to urine.⁷⁵ In a study of pathologic changes in transplanted duodenal tissue from cadaver pancreaticoduodenal grafts, Nakhleh et al. described a variety of conditions (such as epithelial necrosis, crypt loss, reactive atypia, intraepithelial inflammation, and villous atrophy) but no metaplastic or neoplastic changes.⁷⁶ Nghiem et al.⁷⁷ examined graft duodenal biopsies from seven pancreas recipients up to 6 years posttransplant. They observed blunting of the villous epithelium and a variety of chronic inflammatory cellular infiltrates. Of the seven recipients, four showed benign lymphoid aggregates in the lamina propria. One recipient's duodenum showed intestinal metaplasia on days 34, 402, and 558 posttransplant. The natural history of this phenomenon requires further study with longer follow-up times. Filmer and Spencer found the mean time to development of neoplasia in ileal conduits to be 18 years.⁷⁵

Urinary Tract Tumors

The long-term effects of urinary diversion of graft exocrine secretions are not well known, given the relative dearth of long-term follow-up in this population of pancreas recipients. Animal models and clinical experience point to several risk factors that promote transitional epithelial proliferation: altered pH, bacterial overgrowth, chronic bladder irritation, and bladder augmentation with other mucosal surfaces.

The carcinogenic effects of urinary tract infections,⁷⁸ of elevated urinary pH, and changes in urinary sodium and potassium concentrations⁷⁹ have been observed in rats. All these risk factors, as well as chronic chemical irritation by pancreatic enzymes, are found in bladder-drained pancreas recipients. Given the additional setting of chronic immunosuppression, some authors advocate routine cystoscopic evaluation of all recipients after 5 years posttransplant.⁸⁰

Whang et al. reported a single case of multiple adenomas in a recipient's bladder 3 years posttransplant. When the adenomas recurred after endoscopic resection, the recipient underwent enteric conversion with good results.⁸¹ Adenomas have been linked to chronic infection, CMV, and trauma and have occurred after kidney transplants.⁸² They are actually metaplastic lesions with no malignant potential but have been mistaken for well-differentiated adenocarcinomas of the bladder.⁸³

Systemic Tumors

Some solid tumors are clearly associated with the immunosuppressed state and others are more common in solid-organ transplant recipients. Nonetheless, the majority of known malignancies are no more frequent in transplant recipients than in the general population. Skin malignancies, the most com-

TABLE 9.2.5.4. Skin malignancies in pancreas recipients, University of Minnesota, 1989–2001.

Patient	Age at Tx (y)	No. of lesions	Time to diagnosis posttx (y)	Histological findings	Survival (y)	Patient status on Dec 31, 2001
1	37	1	13	M	4	Alive
2	30	1	11	—	6	Dead (other causes)
3	33	1	17	—	2	Alive
4	38	1	17	SC	2	Alive
5	37	2	2, 8	BC, SC	15, 9	Alive
6	33	2	12, 14	SC	3, 2	Alive
7	43	5	4, 4, 6, 9, 10	SC	11, 11, 9, 6, 5	Alive
8	36	1	4	SC	10	Alive
9	41	1	1	SC	11	Dead (other causes)
10	44	1	6	SC	7	Alive
11	33	1	12	SC	2	Alive
12	35	1	8	BC	5	Alive
13	34	2	4, 5	SC	9, 8	Alive
14	24	2	4, 6	BC	7, 5	Alive
15	34	1	3	SC	8	Alive

M, melanoma; SC, squamous cell; BC, basal cell; Tx, transplant.

mon, are 4 to 21 times more likely in transplant recipients than in the general population, with a squamous:basal cell type ratio of 1.75:1. Kaposi's sarcoma, while relatively uncommon, is still 400 to 500 times more likely in transplant recipients, being virtually unknown in the general population.⁸⁴

In the University of Minnesota series, 51 tumors were diagnosed in pancreas recipients. Of these, 23 were skin cancers, including 15 squamous cell carcinomas, 4 basal cell carcinomas, 1 melanoma, and 3 unspecified (Table 9.2.5.4). Of the nonskin tumors, the most common site was the breast, the primary tumor in seven cases (five recipients) (Table 9.2.5.5).

Patient survival with skin malignancies has been uniformly good. From 1978 through 2001, no deaths due to malignancy were recorded. Mean time to diagnosis was 7.7 ± 1.0 years posttransplant. The mean patient survival time since initial diagnosis, censored for nonmalignancy-related deaths, was

7.0 ± 1.2 years. As shown in Table 9.2.5.4, several recipients had multiple skin tumors. In addition, one developed a melanoma followed by carcinoma of the breast; two others developed nonskin tumors (one parotid, one uterine). These three lesions were treated surgically and all three recipients were alive at 2, 4, and 6 years after surgery (as of the end of 2001).

Less favorable prognoses are seen with nonskin solid tumors. As outlined in Table 9.2.5.5, 14 recipients in the University of Minnesota series developed solid tumors. The mean age at transplant was 36.7 ± 1.7 years. These lesions were diagnosed at a mean of 8.0 ± 1.3 years posttransplant (range, 0.5 to 15 years). The majority required surgical therapy, and mean survival time after initial diagnosis was 3.3 ± 0.9 years.

Of note, the University of Minnesota series did not document any cases of Kaposi's sarcoma, even though it accounts

TABLE 9.2.5.5. Nonskin malignancies in pancreas recipients, University of Minnesota, 1989–2001.

Patient	Age at tx (y)	Cancer site	Time to diagnosis posttx (y)	Treatment	Survival (y)	Patient status on Dec 31, 2001
1	37	Breast	15	Surgery, RTX	2	Alive
2	25	Breast	10	Surgery, chemo	3	Dead
3	34	CNS	13	RTX	3	Alive
4	35	GI	10	Surgery, chemo	3	Dead
5	36	GI	11	None	< 1	Dead
6	43	Parotid gland	10	Surgery	4	Alive
7	40	Breast	11	Surgery, RTX	6	Alive
8	34	Breast	8	RTX, chemo	3	Dead
9	42	Testicle (seminoma)	1	Surgery	12	Alive
10	34	Uterus	7	Surgery	7	Alive
11	36	Uterus	7	RTX	2	Alive
12	38	Lung	1	None	<1	Dead
13	50	Oral cavity	<1	Surgery	1	Alive
14	30	Breast	2	Surgery, RTX	2	Alive

RTX, radiation therapy; chemo, chemotherapy; Tx, transplant.

for more than 3% of all neoplasms in solid-organ transplant recipients.⁸⁵ Touraine et al. reported a series of six such patients among their recipients of "kidney and/or pancreas" transplants.⁸⁶ The type of transplant in the six cases was not specified. All six rapidly recovered with reduced immunosuppression, although chemotherapy, surgical resection, radiation, and IFN- α were also used. No patients died of Kaposi's sarcoma, but four developed rejection. Martinenghi et al. reported a series of 9 neoplasms occurring in 7 of 73 kidney-pancreas recipients between 1.5 and 73 months post-transplant.⁸⁷ The cancer-free actuarial survival rate was 92% at 3 years and 85% at 6 years. Their series included two cases of PTLD and one hepatocellular carcinoma (the latter in a recipient with chronic hepatitis C infection). The only two non-skin malignancies in their series were one case of carcinoma of the breast and one case of small-cell carcinoma of the lung.⁸⁷

It is estimated that more than 50% of malignant tumors developing in solid-organ transplant recipients are related to the immunosuppressed state.⁸⁴ Rejection rates are higher in pancreas recipients than in kidney or liver recipients, yet it is unclear if higher doses of immunosuppressive drugs or more aggressive induction protocols result in a higher incidence of neoplastic disease. The bulk of the pancreas transplant experience is recent, and, as these recipients age, malignant tumors will become more common.

In pancreas recipients, the incidence of PTLD is comparable to that in kidney recipients, but its clinical course is markedly more aggressive and survival is decreased. Pancreas recipients appear to have earlier-onset PTLD, as well as a higher proportion of T-cell lesions; this susceptibility may be as much related to the disease as to the innate susceptibility of diabetic transplant recipients. Although rare, solid tumors of the pancreas graft or urinary tract may become more prevalent because of chronic irritation of the duodenum and transitional epithelium. The complete care of pancreas recipients must therefore involve regular surveillance for urothelial and systemic tumors, in particular as graft survival extends past 5 years. A high index of suspicion for these rare yet devastating problems is essential. Proper identification of individuals at risk for PTLD and other forms of malignant disease begins at the time of recipient selection. Increased efforts at monitoring and preventive therapy are currently the only tools to effectively decrease the impact of PTLD and other malignancies.

References

1. Penn I, Brunson ME. Cancers after cyclosporine therapy. *Transplant Proc* 1988;20(3, suppl 3):885.
2. Anagnostopoulos I, Hummel M. Epstein-Barr virus in tumours. *Histopathology* 1996;29:297.
3. Paya CV, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. *ASTS/ASTP*
4. Preiksaitis J, Cockfield S. Epstein-Barr virus and lymphoproliferative disorders after transplantation. In: Bowden R, Ljungman P, Paya C, eds. *Transplant Infections*. Philadelphia: Lippincott-Raven; 1998:245.
5. Sixbey JW, Shirley P, Chesney PJ, Buntin DM, Resnick L. Detection of a second widespread strain of Epstein-Barr virus. *Lancet* 1989;2(8666):761.
6. Rickinson AB, Wallace LE, Epstein MA. HLA-restricted T-cell recognition of Epstein-Barr virus-infected B cells. *Nature* 1980;283(5750):865.
7. Blazar B, Patarroyo M, Klein E, Klein G. Increased sensitivity of human lymphoid lines to natural killer cells after induction of the Epstein-Barr viral cycle by superinfection or sodium butyrate. *J Exp Med* 1980;151:614.
8. Haque T, Thomas JA, Falk KI, et al. Transmission of donor Epstein-Barr virus (EBV) in transplanted organs causes lymphoproliferative disease in EBV-seronegative recipients. *J Gen Virol* 1996;77:1169.
9. Thorley-Lawson DA, Miyashita EM, Khan G. Epstein-Barr virus and the B cell: That's all it takes. *Trends Microbiol* 1996;4:204.
10. Rickinson AB. Epstein-Barr virus in action in vivo. *N Engl J Med* 1998;338:1461.
11. Bourgault I, Gomez A, Gomard E, Levy JP. Limiting-dilution analysis of the HLA restriction of anti-Epstein-Barr virus-specific cytolytic T lymphocytes. *Clin Exp Immunol* 1991;84:501.
12. Goldman M, Velu T. Interleukin-10 and its implications for immunopathology. *Adv Nephrol Necker Hosp* 1995;24:79.
13. Savoie A, Perpete C, Carpentier L, Joncas J, Alfieri C. Direct correlation between the load of Epstein-Barr virus-infected lymphocytes in the peripheral blood of pediatric transplant patients and risk of lymphoproliferative disease. *Blood* 1994;83:2715.
14. Rowe DT, Qu L, Reyes J, et al. Use of quantitative competitive PCR to measure Epstein-Barr virus genome load in the peripheral blood of pediatric transplant patients with lymphoproliferative disorders. *J Clin Microbiol* 1997;35:1612.
15. Oudejans JJ, Jiwa M, van den Brule AJ, et al. Detection of heterogeneous Epstein-Barr virus gene expression patterns within individual post-transplantation lymphoproliferative disorders. *Am J Pathol* 1995;147:923.
16. Starzl TE, Porter KA, Andres G, et al. Long-term survival after renal transplantation in humans (with special reference to histocompatibility matching, thymectomy, homograft glomerulonephritis, heterologous ALG, and recipient malignancy). *Ann Surg* 1970;172:437.
17. Frizzera G, Hanto DW, Gajl-Peczalska KJ, et al. Polymorphic diffuse B-cell hyperplasias and lymphomas in renal transplant recipients. *Cancer Res* 1981;41 (11, pt 1):4262.
18. Nalesnik MA, Jaffe R, Starzl TE, et al. The pathology of post-transplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. *Am J Pathol* 1988;133:173.
19. Locker J, Nalesnik M. Molecular genetic analysis of lymphoid tumors arising after organ transplantation. *Am J Pathol* 1989;135:977.
20. Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: Summary of Society for Hematopathology Workshop. *Sem Diagn Pathol* 1997;14:8.

21. Lippman SM, Grogan TM, Carry P, Ogden DA, Miller TP. Post-transplantation T cell lymphoblastic lymphoma. *Am J Med* 1987; 82:814.
22. Raftery MJ, Tidman MJ, Koffman G, Ogg CS, Macdonald DM, Cameron JS. Posttransplantation T cell lymphoma of the skin. *Transplantation* 1988;46:475.
23. Kumar S, Kumar D, Kingma DW, Jaffe ES. Epstein-Barr virus-associated T-cell lymphoma in a renal transplant patient. *Am J Surg Pathol* 1993;17:1046.
24. Waller EK, Ziemianska M, Bangs CD, Cleary M, Weissman I, Kamel OW. Characterization of posttransplant lymphomas that express T-cell-associated markers: Immunophenotypes, molecular genetics, cytogenetics, and heterotransplantation in severe combined immunodeficient mice. *Blood* 1993;82:247.
25. Sivaraman P, Lye WC. Epstein-Barr virus-associated T-cell lymphoma in solid organ transplant recipients. *Biomed Pharmacother* 2001;55:366.
26. Randhawa PS, Magnone M, Jordan M, Shapiro R, Demetris AJ, Nalesnik M. Renal allograft involvement by Epstein-Barr virus associated post-transplant lymphoproliferative disease. *Am J Surg Pathol* 1996;20:563.
27. Rosendale B, Yousem SA. Discrimination of Epstein-Barr virus-related posttransplant lymphoproliferations from acute rejection in lung allograft recipients. *Arch Pathol Lab Med* 1995;119:418.
28. Drachenberg CB, Abruzzo LV, Klassen DK, et al. Epstein-Barr virus-related posttransplantation lymphoproliferative disorder involving pancreas allografts: Histological differential diagnosis from acute allograft rejection. *Hum Pathol* 1998;29:569.
29. Meador TL, Krebs TL, Cheong JJ, Daly B, Keay S, Bartlett S. Imaging features of posttransplantation lymphoproliferative disorder in pancreas transplant recipients. *AJR* 2000;174:121.
30. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984;1:583.
31. Green M. Management of Epstein-Barr virus-induced post-transplant lymphoproliferative disease in recipients of solid organ transplantation. *Am J Transplant* 2001;1:103.
32. Tsai DE, Hardy CL, Tomaszewski JE, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: Analysis of prognostic variables and long-term follow-up of 42 adult patients. *Transplantation* 2001;71:1076.
33. Armitage JM, Kormos RL, Stuart RS, et al. Posttransplant lymphoproliferative disease in thoracic organ transplant patients: ten years of cyclosporine-based immunosuppression. *J Heart Lung Transplant* 1991;10:877.
34. Cesarman E, Chadburn A, Liu YF, Migliazza A, Dalla-Favera R, Knowles DM. BCL-6 gene mutations in posttransplantation lymphoproliferative disorders predict response to therapy and clinical outcome. *Blood* 1998;92:2294.
35. Faye A, Van Den Abele T, Peuchmaur M, Mathieu-Boue A, Vilmer E. Anti-CD20 monoclonal antibody for post-transplant lymphoproliferative disorders. *Lancet* 1998;352(9136):1285.
36. Iftikharuddin JJ, Miele LA, Rosenblatt JD, Ryan CK, Sahasrabudhe DM. CD-20 expression in post-transplant lymphoproliferative disorders: Treatment with rituximab. *Am J Hematol* 2000;65:171.
37. O'Dwyer ME, Launder T, Rabkin JM, Nichols CR. Successful treatment of aggressive post transplant lymphoproliferative disorder using rituximab. *Leuk Lymphoma* 2000;39(3/4):411.
38. Milpied N, Vasseur B, Parquet N, et al. Humanized anti-CD20 monoclonal antibody (rituximab) in post transplant B-lymphoproliferative disorder: A retrospective analysis on 32 patients. *Ann Oncol* 2000;11(suppl 1):113.
39. Hanel M, Fiedler F, Thorns C. Anti-CD20 monoclonal antibody (rituximab) and cidofovir as successful treatment of an EBV-associated lymphoma with CNS involvement. *Onkologie* 2001; 24:491.
40. Lin JC, Smith MC, Pagano JS. Prolonged inhibitory effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine against replication of Epstein-Barr virus. *J Virol* 1984;50:50.
41. Green M, Reyes J, Webber S, Rowe D. The role of antiviral and immunoglobulin therapy in the prevention of Epstein-Barr virus infection and post-transplant lymphoproliferative disease following solid organ transplantation. *Transplant Infect Dis* 2001;3:97.
42. McDiarmid SV, Jordan S, Kim GS, et al. Prevention and preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver recipients. *Transplantation* 1998;66:1604.
43. Darenkov IA, Marcarelli MA, Basadonna GP, et al. Reduced incidence of Epstein-Barr virus-associated posttransplant lymphoproliferative disorder using preemptive antiviral therapy. *Transplantation* 1997;64:848.
44. Kenagy DN, Schlesinger Y, Weck K, Ritter JH, Gaudreault-Keener MM, Storch GA. Epstein-Barr virus DNA in peripheral blood leukocytes of patients with posttransplant lymphoproliferative disease. *Transplantation* 1995;60:547.
45. Riddler SA, Breinig MC, McKnight JL. Increased levels of circulating Epstein-Barr virus (EBV)-infected lymphocytes and decreased EBV nuclear antigen antibody responses are associated with the development of posttransplant lymphoproliferative disease in solid-organ transplant recipients. *Blood* 1994;84:972.
46. Wagner HJ, Bein G, Bitsch A, Kirchner H. Detection and quantification of latently infected B lymphocytes in Epstein-Barr virus-seropositive, healthy individuals by polymerase chain reaction. *J Clin Microbiol* 1992;30:2826.
47. Stevens SJ, Vervoort MB, van den Brule AJ, Meenhorst PL, Meijer CJ, Middeldorp JM. Monitoring of Epstein-Barr virus DNA load in peripheral blood by quantitative competitive PCR. *J Clin Microbiol* 1999;37:2852.
48. Davis C, Harrison K, McVicar J, Forg P, Bronner M, Marsh C. Antiviral prophylaxis and the Epstein Barr virus-related post-transplant lymphoproliferative disorder. *Clin Transplant* 1995;9:53.
49. Green M, Bueno J, Rowe D, et al. Predictive negative value of persistent low Epstein-Barr virus viral load after intestinal transplantation in children. *Transplantation* 2000;70:593.
50. Rowe DT, Webber S, Schauer EM, Reyes J, Green M. Epstein-Barr virus load monitoring: Its role in the prevention and management of post-transplant lymphoproliferative disease. *Transplant Infect Dis* 2001;3:79.
51. Manez R, Breinig MC, Linden P, et al. Posttransplant lymphoproliferative disease in primary Epstein-Barr virus infection after liver transplantation: The role of cytomegalovirus disease. *J Infect Dis* 1997;176:1462.
52. Davis CL. Interferon and cytotoxic chemotherapy for the treatment of post-transplant lymphoproliferative disorder. *Transplant Infect Dis* 2001;3:108.
53. Davis CL, Wood BL, Sabath DE, Joseph JS, Stehman-Breen C, Broudy VC. Interferon-alpha treatment of posttransplant lymphoproliferative disorder in recipients of solid organ transplants. *Transplantation* 1998;66:1770.

54. Shapiro RS, Chauvenet A, McGuire W, et al. Treatment of B-cell lymphoproliferative disorders with interferon alfa and intravenous gamma globulin. *N Engl J Med* 1988;318:1334.
55. Kane R, Bunchman T, Vogler C, Brems J. Treatment of a B-cell lymphoproliferative disorder in a liver transplant patient with interferon alfa and gamma globulin: A case report. *Clin Transplant* 1992;6:154.
56. Cantarovich M, Barkun JS, Forbes RD, Kosiuk JP, Tchervakov JI. Successful treatment of post-transplant lymphoproliferative disorder with interferon-alpha and intravenous immunoglobulin. *Clin Transplant* 1998;12:109.
57. Walker RC, Marshall WF, Strickler JG, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis* 1995;20:1346.
58. Haque T, Taylor C, Wilkie GM, et al. Complete regression of posttransplant lymphoproliferative disease using partially HLA-matched Epstein Barr virus-specific cytotoxic T cells. *Transplantation* 2001;72:1399.
59. Khanna R, Bell S, Sherritt M, et al. Activation and adoptive transfer of Epstein-Barr virus-specific cytotoxic T cells in solid organ transplant patients with posttransplant lymphoproliferative disease. *Proc Natl Acad Sci USA* 1999;96:10391.
60. Li PK, Tsang K, Szeto CC, et al. Effective treatment of high-grade lymphoproliferative disorder after renal transplantation using autologous lymphocyte activated killer cell therapy. *Am J Kidney Dis* 1998;32:813.
61. Keay S, Oldach D, Wiland A, et al. Posttransplantation lymphoproliferative disorder associated with OKT3 and decreased antiviral prophylaxis in pancreas transplant recipients. *Clin Infect Dis* 1998;26:596.
62. Kroes AC, van der Pijl JW, van Tol MJ, et al. Rapid occurrence of lymphoproliferative disease after pancreas-kidney transplantation performed during acute primary Epstein-Barr virus infection. *Clin Infect Dis* 1997;24:339.
63. Libertiny G, Watson CJ, Gray DW, Welsh KI, Morris PJ. Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients. *Br J Surg* 2001;88:1330.
64. Walker RC, Paya CV, Marshall WF, et al. Pretransplantation seronegative Epstein-Barr virus status is the primary risk factor for posttransplantation lymphoproliferative disorder in adult heart, lung, and other solid organ transplantations. *J Heart Lung Transplant* 1995;14:214.
65. Penn I. Primary kidney tumors before and after renal transplantation. *Transplantation* 1995;59:480.
66. Heinz-Peer G, Helbich T, Barnas U, Mayer G, Muhlbacher F, Mostbeck GH. Renal cell carcinomas of donor origin in two kidney transplants from a single donor. *Transplantation* 1995;59:912.
67. Roza AM, Johnson C, Juckett M, Eckels D, Adams M. Adenocarcinoma arising in a transplanted pancreas. *Transplantation* 2001;72:1156.
68. Barkin JS, Goldstein JA. Diagnostic approach to pancreatic cancer. *Gastroenterol Clin North Am* 1999;28:709.
69. Redmon JB, Teuscher AU, Robertson RP. Hypoglycemia after pancreas transplantation. *Diabetes Care* 1998;21:1944.
70. Tran MP, Larsen JL, Duckworth WC, et al. Anti-insulin antibodies are a cause of hypoglycemia following pancreas transplantation. *Diabetes Care* 1994;17:988.
71. Larsen J, Fellman S, Stratta R. Anti-insulin antibodies may cause hypoglycemia following pancreas transplantation. *Acta Diabetol* 1998;35:172.
72. Dombrowski F, Klingmuller D, Pfeifer U. Insulinomas derived from hyperplastic intra-hepatic islet transplants. *Am J Pathol* 1998;152:1025.
73. Semakula C, Pambuccian S, Gruessner R, Pittenger G, Vinik A, Seaquist E. Hypoglycemia after pancreas transplantation: Association with allograft nesidiodyplasia and expression of islet neogenesis-associated peptide. *J Clin Endocrinol Metab* 2002;87:3548.
74. Rafaeloff R, Pittenger GL, Barlow SW, et al. Cloning and sequencing of the pancreatic islet neogenesis associated protein (INGAP) gene and its expression in islet neogenesis in hamsters. *J Clin Invest* 1997;99:2100.
75. Filmer RB, Spencer JR. Malignancies in bladder augmentations and intestinal conduits. *J Urol* 1990;143:671.
76. Nakhleh R, Gruessner R, Tzardis P, Dunn D, Sutherland D. Pathology of the transplanted human duodenal tissue: A histologic study, with comparison to pancreatic pathology in resected pancreaticoduodenal transplants. *Clin Transplant* 1991;5:241.
77. Nghiem DD, Kessler GM, Olson PR. Effects of long-term exposure to urine on proliferative lesions of the duodenum in bladder-drained pancreas transplants. *Transplant Proc* 1995;27:3004.
78. Davis CP, Cohen MS, Gruber MB, Anderson MD, Warren MM. Urothelial hyperplasia and neoplasia: A response to chronic urinary tract infections in rats. *J Urol* 1984;132:1025.
79. Lina BA, Woutersen RA. Effects of urinary potassium and sodium ion concentrations and pH on *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine-induced urinary bladder carcinogenesis in rats. *Carcinogenesis* 1989;10:1733.
80. Hickey DP, Bakthavatsalam R, Bannon CA, O'Malley K, Corr J, Little DM. Urological complications of pancreatic transplantation. *J Urol* 1997;157:2042.
81. Whang M, Katz L, Ongcapin E, et al. Nephrogenic adenomas occurring in a patient with simultaneous kidney-pancreas transplant. *Urology* 2000;55:949.
82. Beaudry C, Bertrand PE, Laplante L, et al. Nephrogenic adenoma of the bladder after kidney transplantation: Spontaneous improvement with azathioprine removal; surgical trauma and cytomegalovirus infection as possible etiologic factors. *J Urol* 1983;130:1183.
83. Ito TY, Martin DC. Tumors of the bladder in renal transplant patients: Report of a case of adenocarcinoma and review of known cases. *J Urol* 1977;117:52.
84. Penn I. The changing pattern of posttransplant malignancies. *Transplant Proc* 1991;23(1, pt 2):1101.
85. Penn I. Kaposi's sarcoma in organ transplant recipients: Report of 20 cases. *Transplantation* 1979;27:8.
86. Touraine JL, Garnier JL, Lefrancois N, et al. Severe lymphoproliferative disease and Kaposi sarcoma in transplant patients. *Transplant Proc* 1989;21(1, pt 3):3197.
87. Martinenghi S, Dell'Antonio G, Secchi A, Di Carlo V, Pozza G. Cancer arising after pancreas and/or kidney transplantation in a series of 99 diabetic patients. *Diabetes Care* 1997;20:272.
88. Eigidi M, Trofe J, Stratta RJ, et al. Posttransplant lymphoproliferative disorders: Single center experience *Transplant Proc* 2001;33:1838.