Surgical Complications of Pancreas Transplant

Muhammad Irfan Saeed

Contents

Abstract

Pancreas transplantation provides diabetic patients a means of achieving normoglycemia, improving their quality of life and preventing secondary complications of diabetes mellitus. Pancreas transplant is considered a quality of life improving procedure. Compared to liver, heart, and lung transplants which are life-saving procedures, an improved quality of life comes with the cost of potential morbidity related to the operation and the requirement of life-long immunosuppression.

Keywords

Pancreas complications · Graft thrombosis · Urological complications · Acute rejection · PTLD

M. I. Saeed (✉)
Hackensack University Medical Center, Hackensack, NJ, USA
e-mail: irfan_saeed_md@yahoo.com

A. P. Shah et al. (eds.), *Contemporary Pancreas and Small Bowel Transplantation*, Organ and Tissue Transplantation, https://doi.org/10.1007/978-3-319-05257-1_2003

Introduction

Gruessner compared the mortality of pancreas transplant recipients to patients on the pancreas waiting list using data provided by United Network for Organ Sharing (UNOS) and International Pancreas Transplant Registry (IPTR) (Gruessner et al. 2004). Multivariate analysis showed that overall mortality in all three transplant categories (simultaneous pancreas kidney [SPK], pancreas after kidney [PAK], and pancreas transplant alone [PTA]) was not increased after transplantation and was significantly decreased for SPK recipients ($p = <0.001$). Humar studied the incidence of early mortality (less than 3 months after transplant) and demonstrated a significant decrease in the surgical risk associated with this procedure (Humar et al. 1999). Reasons for decreased risk included identification of donor and recipient risk factors, better prophylaxis regimens, surgical technique refinements, and improved immunosuppression. Pancreas transplant patient survival at 1 year and 5 years is currently around 95% and 88%, respectively. Graft survival at 1 year and 5 year is near 85% and 60%, respectively (Gruessner et al. 2011) (Figs. 1, 2, 3, 4, 5, and 6).

Complications after pancreas transplant can be classified as early or late, depending on the timing of onset relative to transplantation (Table 1).

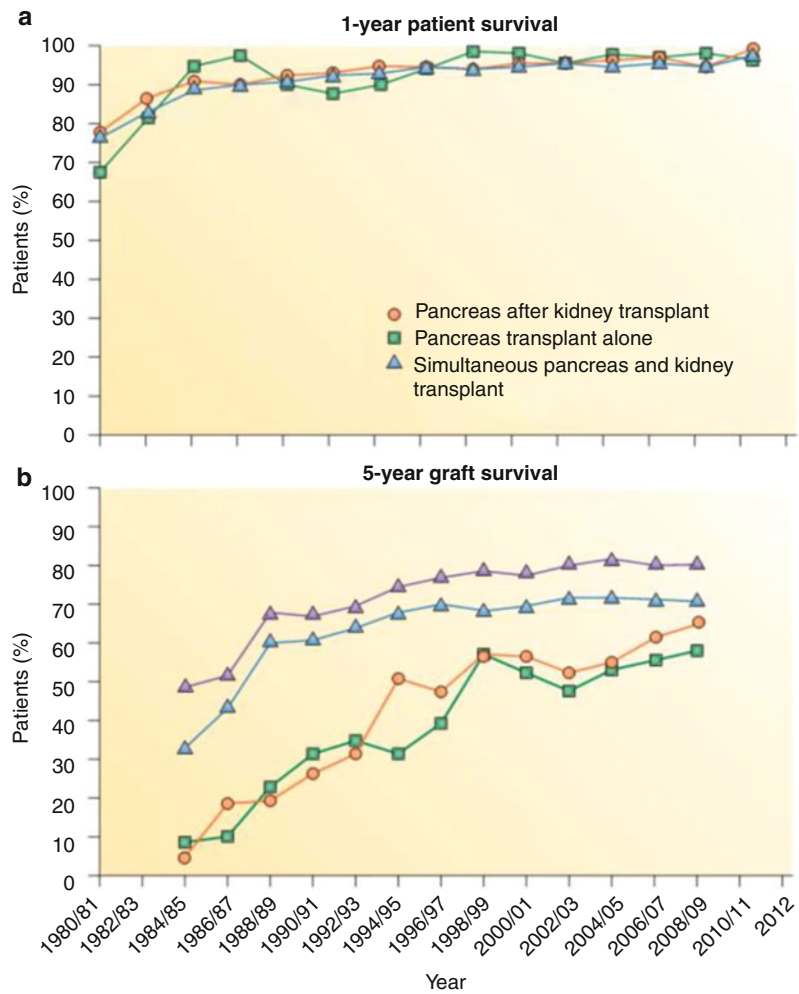

Fig. 1 Patient survival after pancreas transplantation over time. (**a**) 1-year posttransplant survival. (**b**) 5-year posttransplant survival (Data were obtained from the International Pancreas Transplant Registry and the United Network for Organ Sharing)

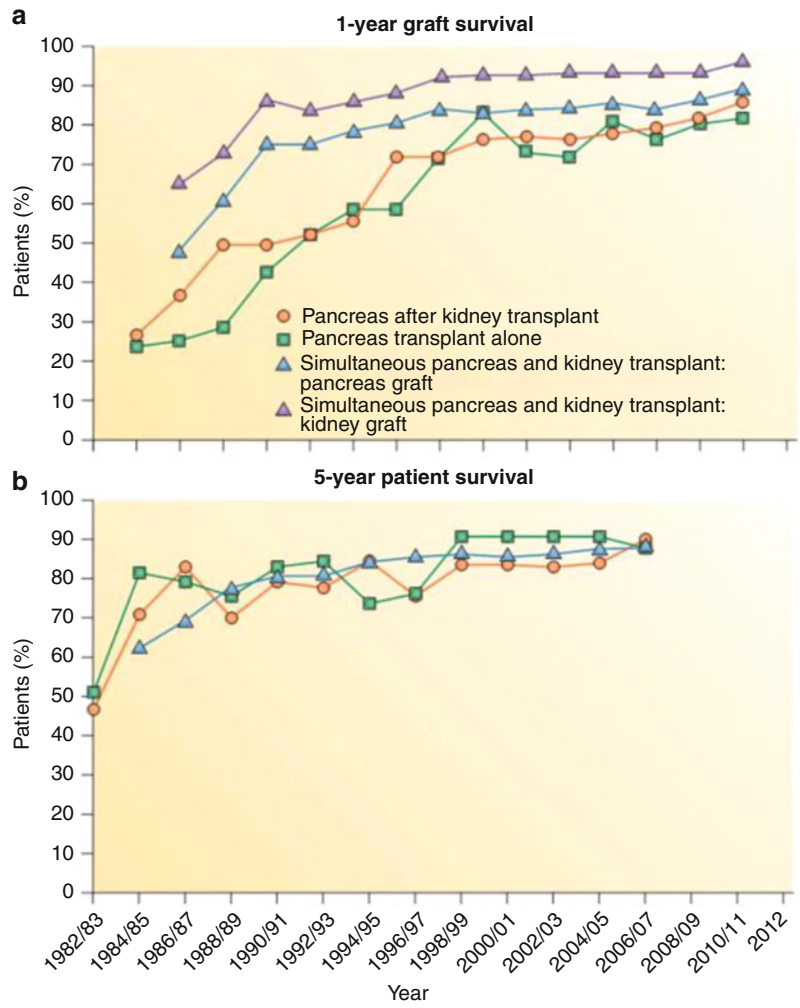

Fig. 2 Pancreas graft survival over time. (**a**) 1-year posttransplant graft survival. (**b**) 5-year posttransplant graft survival (Data were obtained from the International Pancreas Transplant Registry and the United Network for Organ Sharing)

Vascular Complications

Pancreas Graft Thrombosis

Vascular complications include graft thrombosis, arterial stenosis and kinks, pseudoaneurysm formation, arteriovenous fistulae, vessel injury due to surgical technique (clamp injury), and underlying atherosclerotic disease (Chandran et al. 2013). Overall, graft thrombosis incidence ranges from 3% to 10%. The most common reason for early graft loss due to nonimmunological reasons is graft thrombosis.

Both arterial and venous thrombosis are known complications, but venous thrombosis occurs twice as frequently (Farney et al. 2012). Thrombosis can be partial versus complete or early versus late. Risk factors for early pancreas graft thrombosis can be classified in relation to the donor, recipient, or underlying disease (diabetes) (Schenker et al. 2009; Farney et al. 2012). Donor factors include age $>$ 50 years, BMI $>$ 30 kg/m^2, and cardiovascular cause of death (Kandaswamy et al. 2004). Recipient factors included inherited hypercoagulable states, age $>$ 50 years, BMI $>$ 30 kg/m^2, cardiovascular disease, and left-sided graft placement (Kandaswamy et al. 2004; Troppmann et al. 2010; Lubezky et al. 2013). Other factors related to thrombosis are prolonged cold ischemia time greater than 24 h (Parr et al.

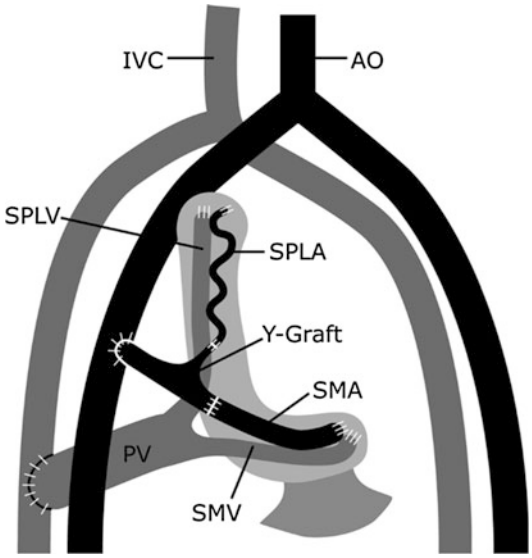

Fig. 3 Surgical arterial anatomy in systemic bladder-drainage pancreatic transplant. As shown, the base of Y graft anastomosis is end-to-side with the recipient common (CIA) or external iliac artery (EIA). The superior mesenteric artery (SMA) perfuses the head and neck of the pancreas, whereas the splenic artery (SPLA) perfuses the body and tail. The relationships with portal vein (PV), superior mesenteric vein (SMV), splenic vein (SPLV), aorta (AO), internal iliac artery (IIA), and inferior vena cava (IVC) are additionally depicted

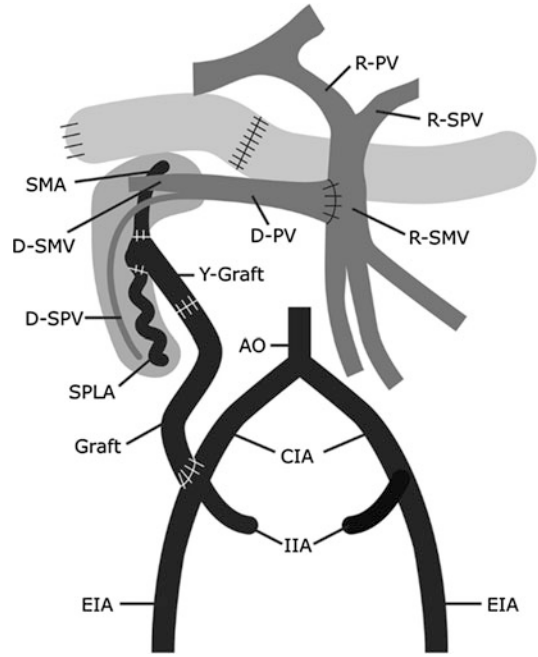

Fig. 4 Surgical arterial anatomy in portal-enteric-drainage pancreatic transplants. As shown, the base of the Y graft anastomosis is end-to-side with the recipient CIA, but it is much longer due to its location in the abdomen. The superior mesenteric artery (SMA) perfuses the head and neck of the pancreas, whereas the splenic artery (SPLA) perfuses the body and tail. The relationships with donor PV (D-PV), donor SMV (D-SMV), donor SPLV (D-SPLV), recipient PV (R-PV), recipient SMV (R-SMV), and recipient splenic vein (R-SPV), aorta (AO), and inferior vena cava (IVC) are additionally depicted

2000), hypotension, segmental pancreas transplant, and postoperative graft pancreatitis (Kandaswamy et al. 2004; Troppmann et al. 2010; Lubezky et al. 2013). Muthusamy explained the pathophysiology of graft thrombosis based on Virchow's triad (Muthusamy et al. 2010) (Table 2).

Diabetes itself is a hypercoagulable state, and many diabetics experience a thrombotic event in their lifetime (Miller 1993; Carr 2001; Wullstein et al. 2003). Furthermore, acute surgical stress induces a transient hypercoagulable state (Muthusamy et al. 2010). Patients with inherited thrombophilic disorders, including deficiencies of natural anticoagulants such as antithrombin III and protein C or S and factor V Leiden and prothrombin mutations, likely contribute to the risk of graft thrombosis (Muthusamy et al. 2010). Endothelial damage leads to a procoagulant milieu and damage can occur secondary to ischemia reperfusion injury. Other factors contributing to graft thrombosis are high dose calcineurin inhibitors (cyclosporine > tacrolimus), type of preservation solution (UW vs. HTK), large flush volume, postoperative pancreatitis, smoking, and obesity. Back-table reconstruction of vessels (arterial) or placement of venous extension graft also contributes to endothelial injury (Farney et al. 2012). Pancreas graft thrombosis is also associated with administration of immunoglobulin IVIG (Sinha et al. 2009). Drainage of the portal vein into the superior mesenteric vein versus a systemic vein (i.e., inferior vena cava versus iliac vein) does not seem to alter the risk of thrombosis. The use of vasopressors was significantly associated with early pancreas graft thrombosis on univariate and multivariate analysis ($p = 0.04$, CI 1.11-68.9) (Schenker et al. 2009).

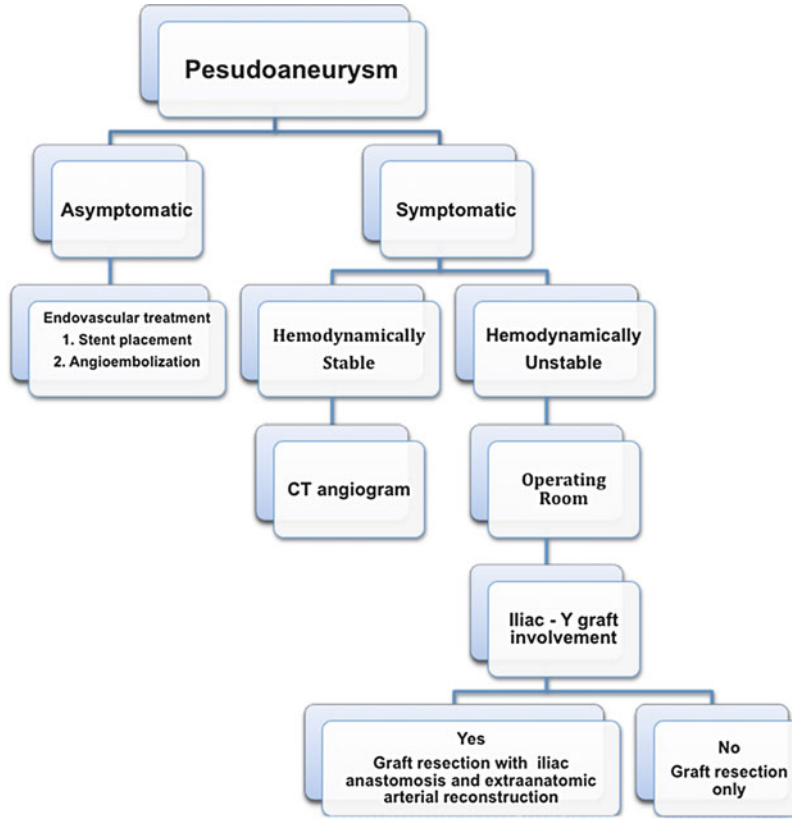

Fig. 5 Management of pseudoaneurysm

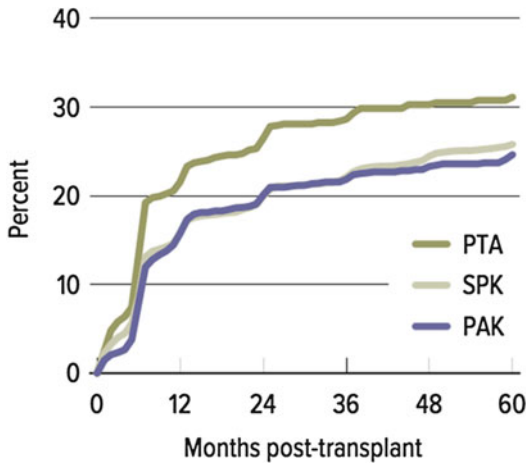

Fig. 6 Incidence of first acute rejection among adult patients receiving a pancreas transplant from 2006 to 2010

Blood glucose concentrations should be monitored frequently during the first 24–72 h after pancreas transplant when risk of thrombosis is highest. A spike in blood sugars suggests the possibility of thrombosis, while elevation of pancreatic enzymes beyond 5 days posttransplant has been cited as an independent risk factor for graft thrombosis (Fertmann et al. 2006). Graft tenderness and enlargement, dark massive hematuria (in bladder-drained pancreas), and markedly decreased urine amylase levels are suggestive of thrombosis (Troppmann et al. 2010). Color Doppler ultrasound is considered the first tool for diagnosis. It is easy to perform and noninvasive, features that make it particularly useful for timely intervention or surveillance of the pancreas graft (Morelli et al. 2008). Each transplant center has its own protocol for surveillance starting from postoperative day 1 and continuing for several days postoperatively. Foshager retrospectively reviewed their center's data and found that absence of antegrade diastolic flow and resistive index (RI) > 1 was 100% sensitive for detection of graft thrombosis (Foshager et al. 1997). Diastolic flow reversal with RI > 1 in the pancreatic allograft artery during the first 12 days after

Table 1 Complications postpancreas transplant

Early	Late
1. Vascular complications	1. Rejection (chronic)
2. Bleeding	2. Vascular complications
3. Leak (intestinal or bladder) anastomosis	3. Intestinal obstruction
4. Rejection	4. Malignancy
5. Graft pancreatitis	5. Infectious complications
6. Infectious complications	6. Immunosuppression
7. Primary nonfunction	
8. Delayed graft function	

Table 2 Factors in pancreas transplant thrombosis classified according to Virchow's triad

Hypercoagulability	Vessel wall changes (endothelial activation)	Changes in flow
Diabetes	Ischemia-reperfusion injury	Altered splenic vein flow dynamics
Surgical stress	Calcineurin inhibitors	Venous outflow (iliac versus caval, left versus right side)
Hyperlipidemia	Overperfusion with preservation solutions	
Inherited thrombophilic disorders	Preexisting vascular disease	
Platelet abnormalities	Pancreatitis	

transplantation was highly specific for venous thrombosis, especially in the absence of venous flow. Computed tomography (CT) and magnetic resonance imaging have also been performed for diagnosis but are less readily available and more costly (Kim et al. 2012). If clinical and radiological data suggest thrombosis, it should be confirmed by angiogram (Friedll et al. 2012) (Table 3).

Most transplant centers utilize some form of anticoagulation for prophylaxis of vascular thrombosis following pancreas transplantation. The choice of anticoagulant, dose, and duration of treatment is typically based upon risk stratification (Fertmann et al. 2006; Farney et al. 2012). Various combinations used include aspirin, dextran (Rheomacrodex, MEDA AS, Denmark), heparin, dipyridamole, and warfarin with varying outcomes (Table 4).

Complete venous or arterial thrombosis generally results in graft loss, but salvage by thrombectomy (surgical or percutaneous) has been described. Partial venous thrombosis (usually of splenic vein) has been managed successfully with anticoagulation alone. Choice of intervention depends upon patient condition (symptomatic versus asymptomatic), site and extent of thrombosis, operator experience, and availability of skilled interventional radiologists (Friedll et al. 2012). Venous thrombosis can propagate beyond the vascular anastomosis; mesenteric venous (if portally drained) and iliac vein or vena cava (if systemically drained) clots should be controlled and cleared to prevent venous insufficiency to the bowel or embolism, respectively (Farney et al. 2012).

Nonmodifiable donor risk factors for pancreas graft thrombosis include age, obesity, vascular disease, and donation after cardiac death. It therefore becomes extremely important to optimize modifiable risk factors like procurement technique, preservation solution (University of Wisconsin), minimization of preservation time, avoidance of high dose calcineurin inhibitors, and meticulous surgical technique. Screening for inherited hypercoagulable states may identify patients at high risk for thrombosis (Wullstein et al. 2003). Postoperative anticoagulation should be utilized, and clinicians should have a low threshold for intervention if thrombosis is suspected (Fridell et al. 2011).

Surgical options for thrombectomy include insertion of a Fogarty balloon catheter through the distal splenic vein or portal vein anastomosis to retrieve the thrombus. Partial pancreatectomy may be a salvage procedure in the setting of a partial thrombus. Endovascular thrombectomy may be attempted for treatment of partial thrombosis (MacMillan et al. 1998; Matsumoto 2011; Saad et al. 2012). Occasionally, surgical intervention is

Table 3 Duplex sonographic criteria for diagnosis of pancreatic transplant venous thrombosis

Sonographic criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Arterial RI $\geq$ 1.00	100	88	69	100
Arterial RI $>$ 1.00	73	95	80	93
Absent intrapancreatic venous flow	100	100	100	100
Arterial RI $\geq$ 1.00 and absent intrapancreatic venous flow	100	100	100	100

Note: *PPV* positive predictive value, *NPV* negative predictive value, *RI* resistive index

Table 4 Anticoagulation measures and thrombosis rates in pancreas transplantation

Source	Intervention	Thrombosis (%)	Bleeding (%)
Sollinger et al.	None	0.8	0.8
Humar et al.	7,500–12,000 U UFH + 325 mg aspirin	6.8	$<$1
Burke et al.	TEG; UFH/aspirin/dextran/warfarin	1	2
Dafoe et al.	Pancreaticorenal composite graft (case report)	–	–
Fertmann et al.	Antithrombin III/IV UFH	16	No difference
Vaidya et al.	TEG; 75 mg aspirin/dextran/UFH/LMWH/ warfarin	0	1.3
Schenker et al.	LMWH	7	6.9

deferred if there is evidence of collateral flow to the pancreas allograft (Kuo et al. 1997; MacMillan et al. 1998; Friedll et al. 2012).

Several investigators have debated the optimal strategy for venous drainage of the pancreas allograft: systemic (via the inferior vena cava or iliac vein) versus portal (via the superior mesenteric vein) (Gaber et al. 1995; Laftavi et al. 2014). Petruzzo compared the two techniques and did not find any significant difference in graft survival, rejection, hyperinsulinemia, or lipid metabolism (Petruzzo et al. 2000). On the contrary, Philosophe concluded that graft survival and rejection were better with portal drainage (Philosophe et al. 2001). These investigators found that systemic drainage caused hyperinsulinemia, which led to accelerated atherosclerosis, independent of the dyslipidemic effects of immunosuppressant.

Bleeding

The impact of postoperative bleeding on graft survival is comparatively benign, as only 0.3% of pancreas grafts are lost secondary to bleeding (Troppmann et al. 2010). Immediate postoperative bleeding is often due to perioperative anticoagulation. Once bleeding or a significant hematoma is diagnosed, the underlying abnormality should be corrected. The recipient should undergo reexploration because a large hematoma can serve as an ideal medium for bacterial growth. A large hematoma can cause external compression on venous outflow or kink the arterial graft. Evacuation of the hematoma can be therapeutic in itself, even if no surgical bleeding is found on reexploration.

Early postoperative vesical bleeding can manifest as hematuria, which is usually self-limiting. Late hematuria is secondary to complications such as graft biopsy or arteriovenous fistula; in those cases most patients will need conversion to enteric drainage (Troppmann et al. 2010). Gastrointestinal bleeding causes in the early and late postoperative period are listed in Table 5. Massive bleeding should be aggressively investigated with a contrast CT scan, and/or emergent intervention (Table 5).

Other Vascular Complications

Besides vascular thrombosis, other vascular complications include development of an arterial pseudoaneurysm, arteriovenous fistula (Dematos

Table 5 Bleeding causes postpancreas transplant

Early postoperative GI bleeding	Late postoperative GI bleeding
1. Duodenal bleeding	1. Ischemic duodenal ulcer
2. Enteric anastomotic	2. Duodenal CMV infection
	3. Acute or chronic duodenal rejection
	4. Duodeno-jejunal anastomosis
	5. Duodenitis
	6. Neoplasm (colonic)
	7. Entero-arterial fistula (massive)

Table 6 Etiological causes of pseudoaneurysm formation

Infectious	Noninfectious
1. Intraabdominal/ wound infection	1. Percutaneous/ transcystoscopic needle biopsy
a. Anastomotic leak (bowel/bladder)	2. Pancreatitis
b. Infected hematoma	3. Procurement injury/back-table injury
c. Wound infection	4. Clamp injury to recipient or donor vessels
d. Bacteremia or candidemia	5. Congenital anomaly

et al. 2000; Barth et al. 2008), arterial stenosis, and arterial dissection (Woo et al. 2003; Tsuchiya 2005). There are no large case series reported on these topics, rather individual case series. A graft pseudoaneurysm can present early (less than 3 months) or late (greater than 3 months) after transplantation. Predisposing factors leading to aneurysm formation are listed in Table 6.

Candida albicans infection can cause inflammatory arteritis, resulting in arterial necrosis (Akhtar et al. 2011). In patients developing infectious complications posttransplant, a Doppler ultrasound of the pancreas transplant is recommended (Kim et al. 2012). Stent placement should not be performed across potentially infected aneurysms due to stent erosion through infected wall and secondary stent infection. An open surgical approach is the preferred treatment for an infected aneurysm with extensive and aggressive toilet of the infected field and extra-anatomic bypass for revascularization (Akhtar et al. 2011). A multidisciplinary approach involving a vascular surgeon is important in managing these complex cases.

Humar et al. found the incidence of deep venous thrombosis (DVT) among SPK and kidney transplant alone patients was 18.1% versus 4.5%, respectively (Humar et al. 1998). In the case of SPK patients, DVTs occurred more commonly on the side of the pancreas versus the kidney allograft. Allen observed two peaks in the timing of thrombosis occurrence: one in the first postoperative month and a second in the fourth month posttransplant (Allen et al. 1987). The second peak most likely represented the time required for resolution of the effect of uremia on erythropoiesis and platelet function. Increased risk of DVT is associated with bilateral dissection of the iliac vessels, longer operative/recovery times, recipient age > 40 years, previous DVT, diabetes mellitus, pelvic dissection, and low flow in the pancreatic venous system. Graduated compression stockings and low dose heparin are routinely recommended for prevention of DVT. Early ambulation is highly recommended postoperatively as well (Humar et al. 1998).

Anastomotic Leak

Anastomotic leaks are responsible for almost 0.5% of all graft losses. The incidence of graft loss is higher with enteric-drained versus bladder-drained pancreas transplants (Troppmann et al. 2010). In enteric-drained pancreas allografts, a leak will present with peritonitis and sepsis due to spillage of enteric contents. In the case of bladder-drained pancreas allografts, leaks are associated with a lower rate of infectious complications.

Symptoms of anastomotic leak include abdominal pain, peritonitis, ileus, fever, leukocytosis, decreased urine output, and hyperamylasemia. Enteric leak can be classified as early (<4 weeks) or late (>4 weeks). Early leaks are usually due to technical failure or ischemia versus late which are due to rejection or infection. Abdominal CT with oral contrast is used to make diagnosis. Treatment includes relaparotomy with

conversion of side-to-side duodeno-jejunostomy to a Roux-en-Y duodeno-jejunostomy. Transplant pancreatectomy is indicated in the presence of diffuse intraabdominal infection or if the patient is unstable.

Bladder-drained graft leaks are divided into early (<4 weeks) and late (>4 weeks). Symptoms are nearly the same as previously described for enteric leaks. CT scan of the abdomen/pelvis with retrograde bladder contrast makes the diagnosis. Low pressure cystography can also be performed, but the former study is more accurate. In early leak cases, prolonged Foley catheter drainage and percutaneous drainage of intraabdominal collections by interventional radiology is therapeutic. If the patient shows signs of peritonitis, then relaparotomy is performed for repair or pancreatectomy. For late leaks, conversion from bladder to enteric-drainage is indicated, irrespective of the etiology (Troppmann et al. 2010).

Graft Pancreatitis

There is no uniformly accepted definition for posttransplant pancreatitis (early or late). Serum markers like amylase and lipase correlate poorly with the severity of graft pancreatitis. Risk factors associated with early postoperative graft pancreatitis include donor quality (age, obesity, history of prolonged resuscitation, excessive inotropic requirements), use of HTK solution (especially when preservation time exceeds >12 h) (Rigley et al. 2008), prolonged preservation time, pancreatic duct outflow impairment, and bladder drainage (reflux pancreatitis). Complications of graft pancreatitis include peripancreatic abscess, pancreatic necrosis (sterile or infected), pancreatic fistulae, pseudocyst, and pseudoaneurysm formation (Akl et al. 2011).

Clinical presentation of graft pancreatitis includes abdominal pain, graft tenderness, nausea, vomiting, ileus, and elevation of serum amylase and lipase. A CT scan with IV contrast of the abdomen/pelvis should be performed to assess the pancreas, for signs of inflammation or necrosis.

Treatment of pancreatitis includes NPO status, bowel rest, and for selected cases, administration of total parenteral nutrition (TPN). The utility of octerotide (a somatostatin analogue) for prevention and treatment remains to be proven. Reflux pancreatitis in bladder-drained pancreas allografts is treated with insertion of a Foley catheter. If repetitive episodes occur, enteric conversion is indicated.

Infections

Postoperative infections can range from superficial wound infections to deep intraabdominal infections. In addition, posttransplant patients are always at risk for bacterial, viral, and fungal infections due to their immunocompromised status (Heitzman et al. 2011).

Superficial wound infections are treated using standard surgical wound care principles. On the other hand, deep wound infections (intraabdominal) present a serious problem. They usually occur within the first 30 days posttransplant. Of all deep infections, 50% are diffuse and 50% are localized. Up to 30% of infections are associated with an anastomotic leak (duodeno-enterostomy or duodeno-cystostomy). Risk factors for intraabdominal infection include older donor age, postoperative bleeding requiring relaparotomy, retransplantation, pretransplant peritoneal dialysis, extended preservation time, graft pancreatitis, and immunosuppression with sirolimus (Heitzman et al. 2011). In clinically stable patients, a CT scan may define the extent and nature of the infection. For bladder-drained grafts, retrograde contrast is used. The differential diagnosis should always include graft thrombosis and anastomotic leak, the treatment options of which were already outlined.

Treatment of the infection depends upon the patient's condition and the underlying cause. If the patient is clinically stable and has a localized intraabdominal infection, then antibiotics with percutaneous drainage is reasonable first-line therapy. If conservative therapy fails, or the patient deteriorates or becomes clinically unstable, relaparotomy is mandatory. If the patient presents with diffuse peritonitis, established surgical principles should be followed with resuscitation, broad-spectrum antibiotics, and surgical

intervention. Decision-making should focus on saving the patient's life versus graft salvage.

The dominant bacterial flora involved in postoperative infections includes Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, and *Morganella morgani*) and Group-D streptococci (*Enterococcus faecium*, *Enterococcus faecalis*). Fungal strains include *Candida* species *C. albicans*, *C. galbrata*, and *C. krusei* (Heitzman et al. 2011). Cytomegalovirus (CMV) mismatch (CMV positive donor to CMV negative recipient) is an independent risk factor for infection. Urinary tract infections are more associated with female sex and bladder drainage of the pancreas graft (Herrero-Martinez et al. 2013). Clinical suspicion should be high for pathogens such as like tuberculosis, *Cryptococcus*, or West Nile virus if the transplant recipient lives in an endemic area.

Primary Nonfunction of Pancreas Graft

Primary nonfunction (PNF) is defined as the absence of graft function after other causes of early graft failure (e.g., vascular graft thrombosis or hyperacute rejection) are ruled out. The reported incidence of PNF is 0.5–1%.

Delayed Graft Function

Delayed graft function (DGF) is defined as the need for transient insulin administration during the early postoperative period; its incidence ranges from 3% to 69%. In the kidney transplant literature, DGF is associated with a higher incidence of rejection. In contrast, the incidence of pancreas transplant rejection is similar for recipients with and without delayed graft function.

Factors associated with DGF are recipient body weight > 80 kg, donor age > 45 years, and cardiocerebrovascular and nontraumatic cause of donor death. Pancreas transplant DGF is a clinical reality but remains poorly understood and warrants further study (Troppmann et al. 2010).

Rejection

Rejection episodes after pancreas transplant are a significant cause for immunological graft loss, though the incidence of rejection has decreased due to new immunosuppressant. The incidence of rejection is highest in pancreas transplant alone (PTA) and lowest in simultaneous pancreas kidney transplant (SPK).

OPTN/SRTR's (Scientific Registry for Transplant Recipients) 2012 annual report showed an increased incidence of acute rejection in PTA as compared to SPK or PAK. One theory that explains the higher incidence of rejection in PTA is that PTA recipients are in a healthier overall state and have a greater ability to mount a strong immune response. Moreover, identification of rejection is more challenging in PTA recipients because rising serum creatinine in SPK patients cannot be used as an early indicator of acute rejection.

Pancreas transplant biopsy is the gold standard for diagnosis of rejection. Drachenberg reviewed histological lesions and criteria for acute cellular and antibody-mediated rejection for pancreas transplant (Drachenberg et al. 2008).

Treatment of acute cellular rejection includes high dose corticosteroids and antithymocyte globulin, while acute antibody-mediated rejection is usually treated with a combination of corticosteroids, plasmapheresis exchange, intravenous immune globulin, and rituximab at most centers. The development of posttransplant donor-specific antibodies is associated with negative outcomes in pancreas transplant outcomes, including graft failure (Akl et al. 2011; Lorentzen et al. 2013; Kremers et al. 2013; Friend et al. 2014).

Malignancy

Solid organ transplant recipients are at increased risk of developing *de novo* malignancies. The most common malignancies include skin cancer, posttransplant lymphoproliferative disorder (PTLD), and Kaposi's sarcoma. Spanogle described the incidence and risk factors for skin cancer in pancreas transplant recipients; at 2, 5,

and 10 years posttransplant, the cumulative incidence of any skin cancer was 4.7%, 12.7%, and 19.6%, respectively (Spanogle et al. 2012). The cumulative incidence of squamous cell carcinoma was 2.8%, 10.3%, and 16.7%, respectively and for basal cell carcinoma was 2.4%, 7.8%, and 17.4%, respectively. Risk factors for skin cancer development include male sex, older age at transplantation, fair complexion, history of nonmelanoma skin cancer (NMSC), infection with the human papillomavirus (HPV), and pretransplantation diseases such as polycystic kidney disease and cholestatic liver disease (Otley et al. 2005; Nordin et al. 2007).

Kaposi's sarcoma, while relatively uncommon, is still 400–500 times more likely to occur in transplant recipients, being virtually absent in the general population.

Prevention is crucial to prevent malignancies in pancreas transplant recipients. This includes reduction in UV exposure (e.g., sun avoidance, UV-protective clothing, and sunscreen use) along with education and self-surveillance. Dermatologic evaluation by a trained health care professional is imperative, especially in patients with a history of skin cancer.

Posttransplant lymphoproliferative disorders include a spectrum of neoplastic diseases ranging from a benign polyclonal lymphoid proliferation resembling infectious mononucleosis to a highly aggressive monoclonal process such as diffuse B-cell lymphoma and disseminated extranodal lymphomas (Kruel et al. 2014). Most cases (80–90%) are of B-cell origin and are associated with Epstein-Barr virus (EBV) infection (Andiman et al. 1985). At least 90% of PTLD cases in solid organ transplants arise from recipient cells, in contrast to PTLD seen after bone marrow transplants (Kruel et al. 2014). PTLD incidence varies depending upon the organ transplanted, ranging from 0.5% in adult kidney or liver transplant recipients to more than 10% in lung, intestinal, and pediatric transplant recipients. As reported in their 2012 annual report, the OPTN/SRTR reported the incidence of PTLD in EBV-negative recipients to be 5%, 2%, and 1.1% in PTA, SPK, and PAK, respectively (Fig. 10). The increased incidence of PTLD in PTA recipients is likely secondary to their increased immunosuppression requirements. Caillard prospectively reviewed PTLD cases between January 1998 and December 2007 and found the cumulative incidence in kidney or kidney-pancreas transplant at 5 and 10 years was 1% and 2.1%, respectively (Caillard et al. 2012).

Risk factors associated with PTLD in a global cohort were age, EBV seronegativity, transplant time (before 2001), SPK transplantation, HLA mismatches, and use of T-cell depleting agents and azathioprine.

The link between EBV and PTLD was established in the early 1980s by Hanto et al. (1982, 1985) and is now widely recognized. The risk for PTLD was much greater in EBV-mismatched pairs (EBV donor/recipient); in contrast, EBV-negative lymphomas were associated with CMV mismatch, arguing for a putative role of another virus. Positive donor CMV serostatus was also associated with a greater risk of brain lymphomas (Caillard et al. 2012). Risk of early onset PTLD (within 12 months of transplant) is twofold higher in recipients with one or two HLA-B mismatches compared to those with no HLA-B mismatch (Caillard et al. 2005). A link between HLA-B mismatch and non-Hodgkin's lymphoma has previously been reported (Verschuuren et al. 2005). Lymphocyte-depleting induction therapy is associated with a 1.4-fold increase in the risk of PTLD. Subgroup analysis revealed that the risk of developing brain lymphomas is particularly high (fourfold higher) in patients who received T-cell depleting agents (Caillard et al. 2012). Cyclosporine was associated with an increased risk of graft lymphoma (RR = 2.7) but not with other types of PTLD. Azathioprine was associated with the development of lymphomas, particularly graft PTLD and EBV-positive lymphoproliferations. WHO classification of PTLD is shown in Fig. 8 (Taylor et al. 2005) (Figs. 7, 8, and 9).

Presenting symptoms of PTLD may be mild, resembling a mononucleosis-like syndrome (e.g., malaise, sweats, and fever). Unintentional weight loss and palpable or identifiable lymphadenopathy should prompt a biopsy, as histological analysis is key to diagnosis.

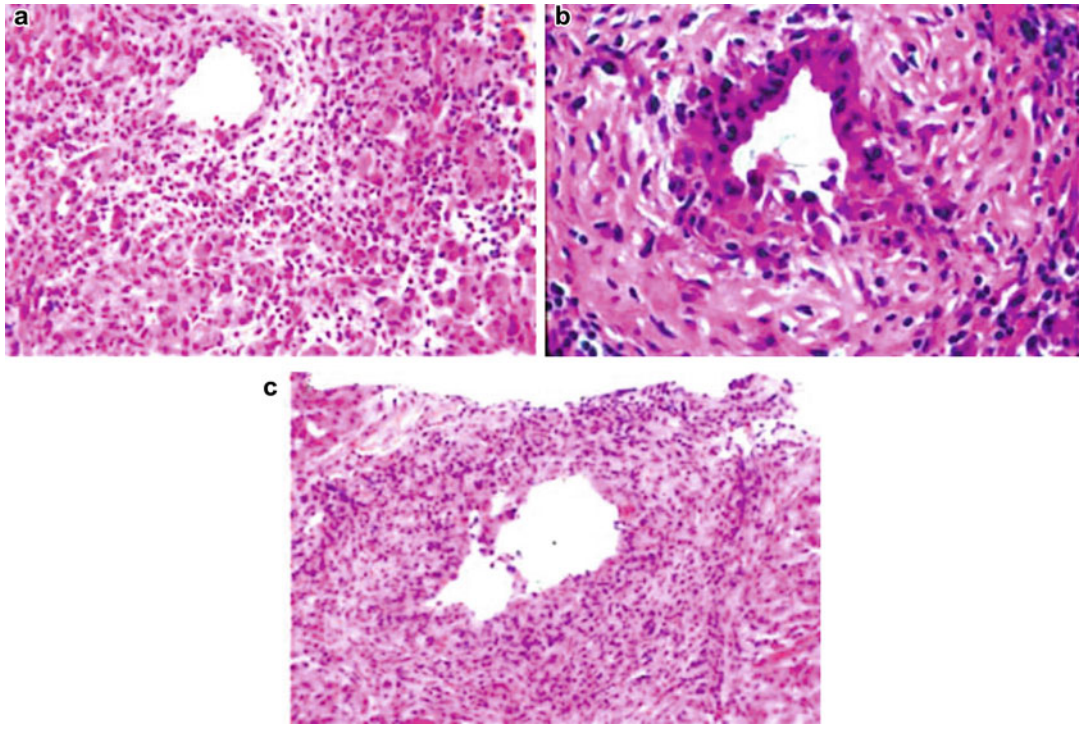

Fig. 7 Acute cell-mediated rejection (ACMR). (**a**) Active septal inflammation with numerous eosinophils and venulitis (*upper middle field*). (**b**) Ductal inflammation and associated reactive/regenerative epithelial changes. (**c**) Severe ductal inflammation. Dense infiltrates around a duct with extensive denudation of its epithelial lining. Few epithelial clusters on the *left upper contour* were positive for cytokeratin stain (not shown)

Treatment of early stages of PTLD may be effectively accomplished by reducing or discontinuing immunosuppression. Antiviral therapy with ganciclovir is controversial; however, other types or advanced stages of PTLD may require chemotherapy, radiation therapy, B-cell directed antibodies (e.g., rituximab), or resection.

Caillard reported graft survival of patients with lymphoma at 1 and 5 years to be 88% and 60%, respectively with treatment (Caillard et al. 2012). Overall PTLD patient survival was 73%, 60%, and 55% at 1, 5, and 10 years, respectively. Parasekevas compared the outcomes of PTLD in pancreas transplant recipients (n = 1357) to liver and kidney transplant recipients and found that pancreas transplant recipients had a significantly shorter survival ($p = 0.001$) (Paraskevas et al. 2005). Malignancies were more aggressive in pancreas recipients, with a higher stage at presentation and a trend toward more bone marrow involvement.

Hickey and associates advocate regular cystoscopic follow-up to rule out bladder cancer in all recipients of bladder-drained pancreatic transplants for 5 years posttransplant. Surgical therapy of bladder cancer should be aggressive (radical surgery with or without neoadjuvant/adjuvant radiotherapy and/or chemotherapy) and performed expeditiously (Highshaw et al. 2002).

Urological Complications

Urological complications after bladder drainage of the pancreas graft can be defined as directly related to the operation or indirectly related to the effect of pancreas transplantation on the lower urinary tract system (Gettman et al. 1996; Ciancio et al. 2000). Table 7 lists the urological complications found in pancreas transplantation.

Blanchet found a correlation between preoperative urodynamic abnormalities and the

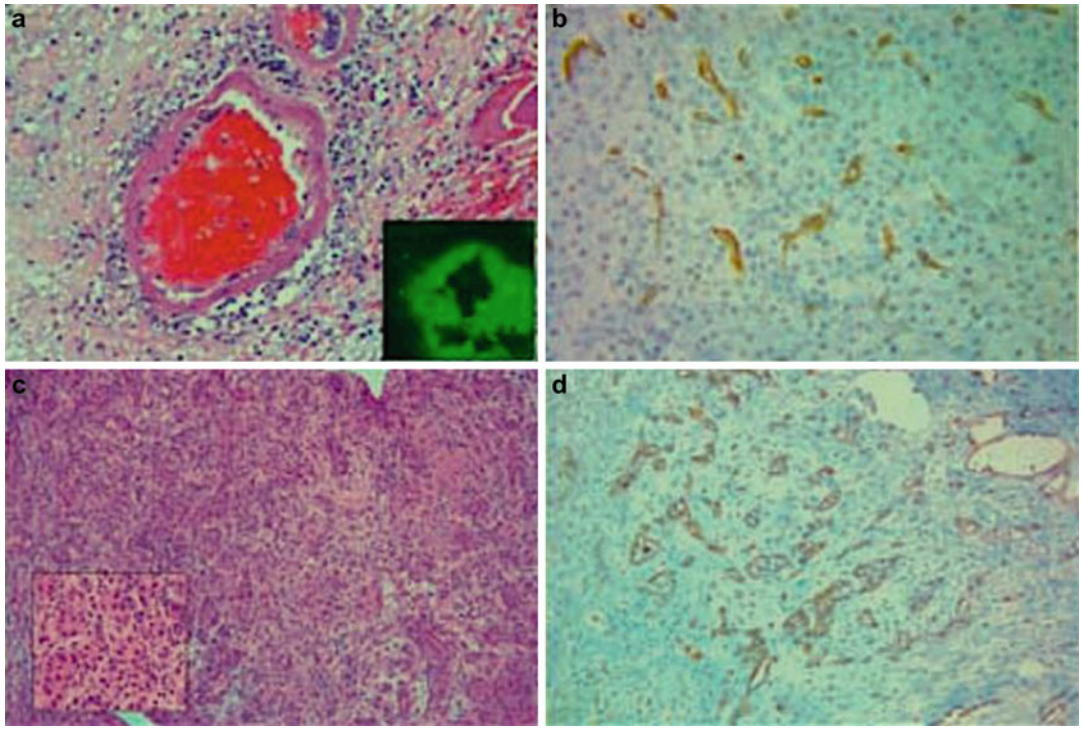

Fig. 8 Antibody-mediated rejection (ABMR). (**a**) Arterial fibrinoid necrosis due to accelerated AMR in a graft pancreatectomy performed 30 h posttransplantation. Insert: immunofluorescence stain is strongly positive for IgG. C4d stain (not represented) was also positive in all size vessels. (**b**) C4d stain in pancreatic capillaries in patient with acute AMR biopsied 10 days posttransplantation. (**c**) Same patient as part B, biopsied 18 days posttransplant, continues to have strong positivity for C4d (not represented) and extensive interacinar neutrophilic inflammation. Note foci of necrosis (*upper right*). (**d**) Same patient as parts B and C: strong C4d staining in pancreas lost due to persistent AMR, 3 months posttransplantation. Note extensive fibrosis with associated obliteration of the endocrine and exocrine components (chronic active AMR)

development of urological complications (Blanchet et al. 2003). Urodynamic abnormalities included large bladder capacity and a highly noncompliant and hypocontractile bladder with impaired proprioception and flow with postvoid residual urine. Gettman noted that criteria for abnormal preoperative urodynamics included detrusor hyperreflexia or areflexia (Gettman et al. 1996). Hyperreflexia is defined as uninhibited detrusor contraction with detrusor pressures of 15 cm H_2O or greater. Detrusor areflexia was defined as absent detrusor contractions or low pressure contractions accompanied by straining or stop-start voiding with a bladder volume of $>$ 600 cm^3, maximum flow less than 10 cm^3/s, and residual urine $>$ 150 cm^3. Indeterminate findings were defined as inconclusive detrusor pressures with normal bladder volume and maximum flow less than 10 cm^3/s and poor compliance or increased detrusor pressure 20 cm H_2O or greater over time without detrusor contraction.

Urinary tract infections are the most common urological complications with bladder-drained pancreas transplants. The most common organisms include *E. coli*, Group-D *Enterococcus*, *Staphylococcus epidermidis*, *Pseudomonas species*, *Proteus mirabilis*, or *Candida species* (Gettman et al. 1996). Patients are treated with intravenous or oral antibiotics depending on organism susceptibilities. Recurrent urinary tract infections can lead to drug resistance and frequent hospital readmissions.

Hematuria can be microscopic or gross and present early ($<$4 weeks) or late ($>$4 weeks)

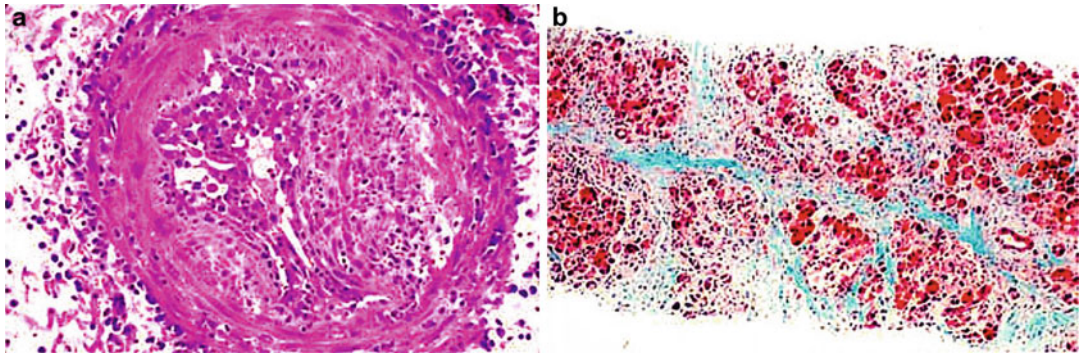

Fig. 9 Chronic rejection/graft sclerosis. (**a**) Artery with severe luminal narrowing due to a combination of acute (intimal arteritis) and active chronic cell-mediated allograft rejection. The latter appears as two 'cushion-like' areas of intimal fibrosis with mononuclear inflammation. (**b**) Stage II of chronic rejection/graft sclerosis characterized by septal and acinar fibrosis that extends to the center of the acinar lobules

Table 7 Urological complications after pancreas transplant

Urinary tract infection	39–58%
Hematuria	11–26%
Graft pancreatitis	19–26%
Duodenal leaks	7–17%
Urethral complications (urethritis, disruptions)	2–3%
Calculi	2.5–5%

posttransplant. Causes of hematuria include anastomotic bleeding (suture or staple line), duodenitis, urinary tract infection (UTI), postbiopsy, cytomegalovirus infection, reflux pancreatitis, rejection, bladder calculi, and pseudoaneurysm (Esterl et al. 1995; Polo et al. 2009). Treatment for the review etiologies includes Foley catheterization, bladder irrigation, clot evacuation, cystoscopy with fulguration of duodeno-vesical anastomosis, and surgery (Gettman et al. 1996).

Graft pancreatitis after bladder-drained pancreas transplant presents with diffuse abdominal pain, graft tenderness, nausea, vomiting, and irritative voiding. Lab results reveal hyperamylasemia and sometimes concurrent urinary tract infections. Preoperative urodynamic evaluation may show detrusor areflexia or hyperreflexia. Abdominal ultrasound or computerized tomography is diagnostic in majority of cases. Treatment includes Foley catheterization, bowel rest, intravenous fluids, and antibiotics for concurrent urinary tract infections, if present. Enteric drainage conversion is recommended in patients with severe or recurrent episodes of reflux pancreatitis (Gettman et al. 1996).

Duodenal leak presents similarly to graft pancreatitis with abdominal pain and graft tenderness. Early leaks are mainly due to technical reasons or ischemia and can be small and asymptomatic. Late duodenal leaks are a result of ulceration, CMV infection, or chronic inflammation (Polo et al. 2009). CT scan and cystoscopy in bladder-drained cases are used to diagnose a duodenal leak. Small asymptomatic leaks can be treated with Foley catheterization, while leaks which present with peritonitis are managed with exploratory laparotomy.

Urethral complications are presumably related to drainage of exocrine pancreatic secretions through the bladder. The patient usually presents with irritative voiding symptoms, penile pain, and perineal discomfort. Urethritis usually resolves after short-term Foley catheterization. Calculus formation can also occur in the bladder-drained pancreas allograft. Nonabsorbable sutures or a surgical staple can act as a nidus within the bladder for calculus formation (Polo et al. 2009). Patient with bladder drainage sometimes have to take oral sodium bicarbonate to prevent chronic metabolic acidosis (intractable) secondary to exocrine pancreatic secretions (Figs. 10, 11, and 12).

Cystoenteric conversion rate is reported between 6% and 23% (Stephanian et al. 1992; Kleespies 2011). Major indications for conversion include chronic urinary tract infection, recurrent

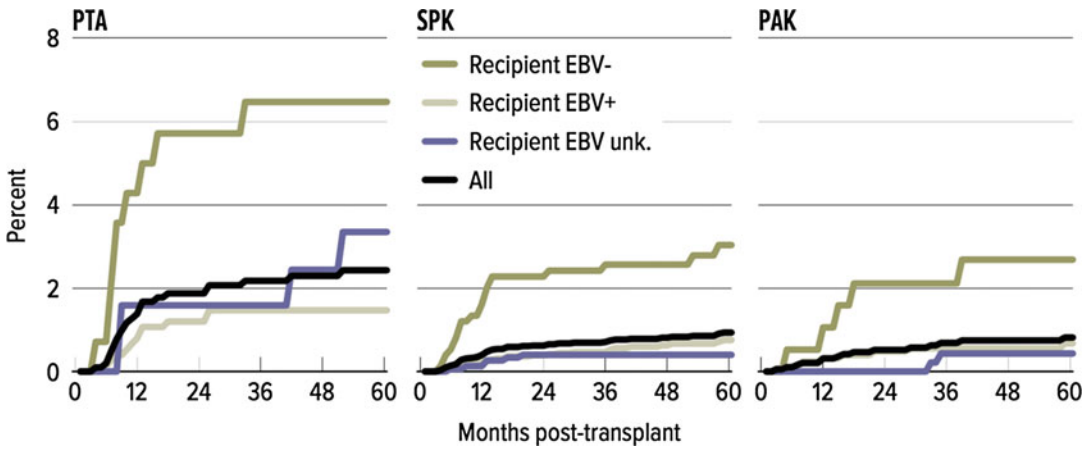

Fig. 10 Incidence of PTLD (posttransplant lymphoproliferative disorder) among adult pancreas transplant recipients 2006–2010, by recipient Epstein-Barr virus (EBV) status

Fig. 11 WHO classification of PTLD (posttransplant lymphoproliferative disorder

Category	Subtype
Early lesions	Reactive plasmacytic hyperplasia
Polymorphic PTLD	Polyclonal Monoclonal
Monomorphic PTLD	B-cell lymphomas Diffuse large B-cell lymphoma Burkitt's/Burkitt's-like lymphoma Plasma cell myeloma T-cell lymphomas Peripheral T-cell lymphoma Rare types (gamma/delta, T/natural killer cell) Other types Hodgkin's disease-like Plasmacytoma-like

reflux pancreatitis, chronic intractable metabolic acidosis, and urethritis. Complications related to enteric drainage conversion include anastomotic leak, pancreatitis, duodenal perforation, and intraabdominal infection. One important risk factor is the development of rejection after enteric-drainage conversion, which can lead to graft loss in almost 15% of recipients (Jimenez-Romero et al. 2009). Some authors have recommended waiting at least 1 year after the last rejection episode before converting to enteric drainage; however, other series have not shown any difference in rejection episodes after conversion (Jimenez-Romero et al. 2009).

Enteric drainage and bladder drainage pancreas transplants have similar patient and graft survival (Gruessner et al. 2011). The rate of enteric drainage has significantly increased, and more than 80% of pancreas transplant recipients now have enteric drainage versus bladder drainage as shown in Fig. 12.

Miscellaneous

The incidence of pancreatic pseudocyst formation is reported to be less than 10% but is difficult to determine, as not every pancreatic fluid collection

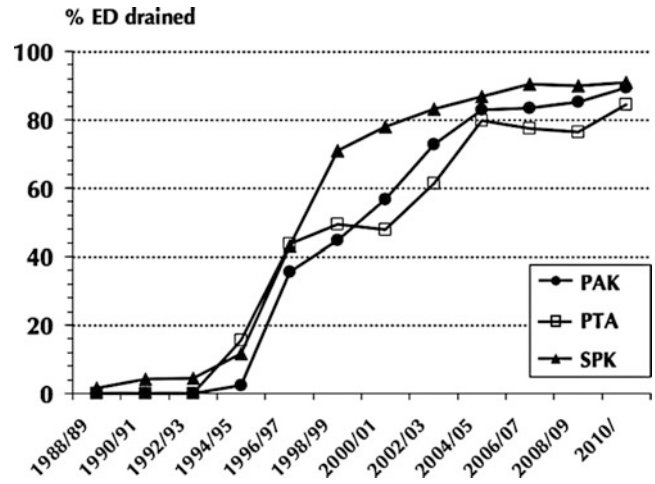

Fig. 12 Rate of enteric drainage in pancreas transplantation in the USA, 1988–2010. *ED* enteric drainage (Gruessner et al. 2011)

is a true pseudocyst. The diagnosis can be made by ultrasound, CT scan, or MRI. If imaging studies are equivocal (e.g., in the case of a complex pseudocyst with multiple septations and an inhomogeneous appearance), a pseudocyst can be differentiated by amylase levels in the aspirate. All symptomatic and large asymptomatic peripancreatic fluid collections should be drained. More aggressive treatment is indicated from the outset in the case of complications, namely hemorrhage, cyst perforation, or a symptomatic pseudocyst that is refractory to repetitive nonoperative intervention. For bladder- and enteric-drained grafts, internal drainage may involve creating a cyst jejunostomy. A cyst cystostomy can be performed in the case of a bladder-drained pancreas. Graft pancreatectomy in these cases should rarely be employed except in unusual circumstances such as complicated 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 into large pancreatic or peripancreatic blood vessels.

Conclusion

Careful selection of donor and recipient, meticulous surgical technique, and high clinical suspicion can prevent and decrease surgical complications.

Acknowledgments Special thanks to Jaclyn McKeen, Pharm.D., BCPS; Richard Ruiz, M.D., FACS; Marlon Levy, M.D., FACS; and Goran Klintmalm, M.D., Ph.D., FACS in preparation of this book chapter.

References

Akhtar MZ, Jones A, Sideso E, Sinha S, Vaidya A, Darby C (2011) Management of a ruptured mycotic pesudoaneurysm following pancreas-kidney transplantation. Ann Transplant 16(4):122–125

Akl A, Cantarovich D, De Amicis S et al (2011) Posttransplant donor-specific anti-HLA antibodies negatively impact pancreas transplantation outcome. Am J Transplant 11:2737–2746

Allen RD, Mite CA, Moor JA, Morris PJ (1987) Deep venous thrombosis after renal transplantation. Surg Gynecol Obstet 164:137

Andiman W, Ho M, Miller G, Atchison RW, Breinig MK, Dummer JS, et al (1985) Epstein-Barr virus infections and DNA hybridization studies in post transplantation lymphoma and lymphoproliferative lesions: the role of primary infection. J Infect Dis 152:876–886

Barth MM, Khwaja K, Faintuch S, Rabkin D (2008) Transarterial and transvenous embolotherapy of arteriovenous fistulas in the transplanted pancreas. J Vasc Interv Radiol 19:1231–1235

Blanchet P, Droupy S, Eschwege P, Hammoudi Y, Durrbach A, Charpentier B, Benoit G (2003) Urodynamic testing predicts long-term urological complications following simultaneous pancreas-kidney transplantation. Clin Transplant 17:26–31

Bloom RD, Olivares M, Rehman L, Raja RM, Yang S, Badosa F (1997) Long-term pancreas allograft outcome in simultaneous pancreas-kidney transplantation: a comparison of enteric and bladder drainage. Transplantation 27:1689

Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K (2005) Post-transplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 80:1233–1243

Caillard S, Lamy FX, Quelen C, Dantal J, Lebranchu Y, Lang P, Velten M, Moulin B (2012) Epidemiology of post transplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am J Transplant 12:682–693

Carr ME et al (2001) Diabetes mellitus: a hypercoagulable state. J Diabetes Complicat 15:44

Chandran S, Kanellis J, Polkinghorne K, Saunder A, Mulley W (2013) Early pancreas allograft thrombosis. Clin Transplant 27:410–416

Chapman JR, Robertson P, Allen RDM (2001) Analysis and commentary. Why does pancreas transplants thrombose? Transplantation 72:182

Ciancio G, Lo Monte A, Julian JF, Romano M, Miller J, Burke GW (2000) Vascular complications following bladder drained, simultaneous pancreas-kidney transplantation: the University of Miami experience. Transplant Int 13(1):187–190

Del Pizzo JJ, Jacobs SC, Bartlett ST, Sklar GN (1998) Urological complications of bladder-drained pancreatic allografts. Br J Urol 81:543–547

Dematos A, Paduch DA, Conlin M et al (2000) Arterial duodenovesical fistula after simultaneous pancreas and kidney transplantation. J Urol 164(4):1296

Drachenberg CB, Odorico J, Demetris AJ et al (2008) Banff Schema for grading pancreas allograft rejection: working proposal by a multi-disciplanary international consensus panel. Am J Transplant 8:1237–1249

Egidi MF, Trofe J, Stratta RJ, Flax SD, Gaber LW, Shokouh-Amiri MH, Jones M, Vera SR, Alloway RR, Gaber AO (2001) Post transplant lymphoproliferative disorders: a single center experience. Transplant Proc 33:1838–1839

Esterl RM, Stratta JR, Taylor RJ, Radio SJ (1995) Rejection with duodenal rupture after solitary pancreas transplantation: an unusual cause of severe hematuria. Clin Transplant 9:155–159

Farney AC, Rogers J, Stratta R (2012) Pancreas graft thrombosis: causes, prevention, diagnosis, and intervention. Curr Opin Organ Transplant 17:87–92

Fertmann JM, Wimmer C, Arbogast H, Illner W, Tarabichi A, Calasan I, Dieterle C, Land W, Jauch K, Johannes N (2006) Single shot antithrombin in human pancreas-kidney transplantation: reduction of reperfusion pancreatitis and prevention of graft thrombosis. Transpl Int 19:458–465

Finger FB, Radosevich D, Dunn T, Chinnakotla S, Sutherland D, Matas A, Pruett T, Kandaswamy R (2013) A composite risk model for predicting technical failure in Pancreas transplantation. Am J Transplantat 13:1840–1849

Foshager MC, Hedlund LJ, Troppmann C, Benedetti E, Gruessner RW (1997) Venous thrombosis of pancreatic transplants: diagnosis by duplex sonography. AJR Am J Roentgenol 169:269–1273

Fridell JA, Mangus RS, Mull AB, Taber TE, Sanders CE, Slisher RC, Goble ML, Powelson JA (2011) Early reexploration for suspected thrombosis after pancreas transplantation. Transplantation 91:902–907

Friedll JA, Johnson M, Goggins W, Beduschi T, Mujtaba M, Goble M, Powelson J (2012) Vascular catastrophes following pancreas transplantation: an evolution in strategy at a single center. Clin Transplant 26:164–172

Gaber AO, Shokouh-Amiri MH, Hathaway DK (1995) Results of pancreas transplantation with portal venous and enteric drainage. Ann Surg 221:613

Garcia-Roca R, Samame J, Garcia-Criado M, Real M, Gilbert R, Ricart M (2012) Preservation of pancreas graft function after complete venous thrombosis: report of four cases treated conservatively. Transplantation 93:214–218

Gettman MT, Levy JB, Engen DE, Nehra A (1996) Urological complications after kidney – pancreas transplantation. J Urol 159:38–43

Green BT, Tuttle-Newjall J, Suhocki P et al (2004) Massive gastrointestinal haemorrhage due to rupture of a donor pancreatic artery pesudoaneurysm in a pancreas transplant patient. ClinTranspl 18:108–111

Gritsch HA, Shapiro R, Egidi F, Randhawa P, Starzl T, Corry R (1997) Spontaneous arterioenteric fistula after pancreas transplantation. Transplantation 63(6): 903–904

Gruessner RW, Sutherland D, Gruessner A (2004) Mortality assessment for pancreas transplants. Am J Transplant 4:2018–2026

Gruessner A et al (2011) 2011 Update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). Rev Diabet Stud 8:6–16

Hampson FA, Freeman S, Ertner J, Drage M, Butler A, Watson C, Shaw A (2010) Pancreatic transplantation: surgical technique, normal radiological appearances and complications. Insights Imaging 1:339–347

Hanto DW, Frizzera G, Gajl-Peczalska KJ et al (1982) Epstein-Barr virus induced B-cell lymphoma after renal transplantation: acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. N Engl J Med 306:913–918

Hanto DW, Frizzera G, Gajl-Peczalska KJ, Simmons RL (1985) Epstein-Barr virus immunodeficiency, and B cell lymphoproliferation. Transplantation 39:461–472

Heitzman M, Ziaja J, Krol R, Chudek J, Pawlicki J, Kolonko A et al (2011) Intra-abdominal infections after simultaneous pancreas-kidney transplantation. Ann Transplant 16(3):36–43, Epub 2011/10/01

Herrero-Martinez JM, Lumbreras C, Manrique A, San-Juan R, Garcia-Reyne A, Lopez-Medrano F, Lizasoain M, De Dios B, Andres A, Jimenez C, Gutierrez E, Moreno E, Aguado JM (2013) Epidemiology, risk factors and impact on long-term pancreatic

function of infection following pancreas-kidney transplantation. Clin Microbiol Infect 19:1132–1139
Highshaw RA, Tunuguntla H, Perez RV, Gandour-Edwards R, Evans CP (2002) Initial report of bladder carcinoma following combined bladder-drained pancreas and kidney transplantation. Clin Transplant 16:383–386
Humar A, Johnson EM, Gillingham KJ, Sutherland DE, Payne WD, Dunn DL, Wrenshall LE, Najarian JS, Gruessner RW, Matas AJ (1998) Venous thromboembolic complications after kidney and kidney-pancreas transplantation. Transplantation 65(2):229–234
Humar A, Kandaswamy R, Granger D, Gruessner R, Gruessner A, Sutherland D (1999) Decreased surgical risks of pancreas transplantation in the modern era. Ann Surg 231(2):269–275
Humar A, Ramcharan T, Kandaswamy R, Gruessner R, Gruessner A, Sutherland D (2004a) Technical failures after pancreas transplants: why graft fail and the risk factors – a multi – variate analysis. Transplantation 78:1188–1192
Humar A, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AG, Sutherland DE (2004b) The impact of donor obesity on outcomes after cadaver pancreas transplants. Am J Transplant 4:605
Ito T, Fumimoto Y, Tanemura M, Hoshida Y, Nishida T, Sawa Y (2008) Graft duodenal perforation due to internal hernia after simultaneous pancreas-kidney transplantation: report of a case. Case Rep Gastroenterol 2:244–249
Izaki K, Yamaguchi M, Matsumoto I et al (2011) Percutaneous selective embolectomy using a fogarty thru-lumen catheter fro pancreas graft thrombosis: a case report. Cardiovasc Intervent Radiol 34:650–653
Jimenez-Romero C, Manrique A, Morales JM, Lopez RM, Morales E, Cambra F, Calvo J (2009) Conversion from bladder to enteric drainage for complications after pancreas transplantation. Transplant Proc 41:2469–2471
Kandaswamy R, Humar A, Gruessner A et al (1999) Vascular graft thrombosis after pancreas transplantation: comparison of the Fk and CsA era. Transplantation 31:602
Kandaswamy R, Humar A, Ramcharan T et al (2004) The impact of donor obesity on outcomes after cadaver pancreas transplants. Am J Transplant 4:611
Khaja M, Matsumoto A, Saad W (2014) Vascular complications of transplantation: part 2: pancreatic transplants. Cardiovasc Intervent Radiol 37:1415–1419
Khan TF, Ciancio G, Burke GW et al (1999) Pesudoaneurysm of the superior mesenteric artery with an arteriovenous fistula after simultaneous kidney-pancreas transplantation. Clin Transplant 13(3): 277–279
Kim YH, Park J, Lee S, Byun J, Kim S, Han D (2012) How to avoid graft thrombosis requiring graftectomy: immediate posttransplant CT angiography in pancreas transplantation. Transplantation 94:925–930
Kimura T, Saito T, Tsuchiya A et al (2005) Treatment of external iliac artery dissection with endovascular stent placement in a patient with simultaneous pancreas and kidney transplantation. Transplant Proc 37:3572–3573
Kleespies A, Mikhailov M, Khalil P, Preissler G, Rentsch M, Arbogast H, Illner W-D, Burns C, Jauch K-W, Angele MK (2011) Enteric conversion after pancreatic transplantation: resolution of symptoms and long term results. Clin Transplant 25:549–560
Kremers W, Dong M, Parsaik AK et al (2013) Acute pancreas allograft rejection is associated with increased risk of graft failure in pancreas transplantation. Am J Transplant 13:1019–1025
Kruel CR, Ruiz RM, Shiller M, Anthony T, Goldstein R, Kim P, Levy ML, McKenna GJ, Onaca N, Testa G, Klintmalm GB (2014) Posttransplant lymphoproliferative disorder presenting as a small bowel obstruction in a patient with pancreas transplantation alone. Proc (Bayl Univ Med Cent) 27(4):346–348
Kuo PC, Wong J, Schweitzer E, Johnson LB, Lim J, Bartlett S (1997) Outcome after splenic vein thrombosis in the pancreas allograft. Transplantation 64(6):933–935
Laftavi MR, Pankewycz O, Kohli R, Feng L, Said M, Sharma R, Patel S (2014) Short and long term outcomes of systemic drainage to IVC: a new technique for pancreas transplantation. Transpl Proc 46:1900–1904
Lorentzen DF, Niederhaus SV, Leverson GE et al (2013) Acute cellular and anti-body mediated rejection of the pancreas allograft: incidence, risk factors and outcomes. Am J Transplant 13:2945–2955
Lubezky N, Goykhman Y, Nakache R, Kessler A, Baruch R, Katz P, Kori I, Klausner J, Ben-Haim M (2013) Early and late presentations of graft arterial pesudoaneurysm following pancreatic transplantation. World J Surg 37:1430–1437
Lumbreras C, Fernandez I, Velosa J, Munn S, Sterioff S, Paya CV (1995) Infectious complications following pancreatic transplantation: incidence, microbiological and clinical characteristics, and outcome. Clin Infect dis 20:514–520
MacMillan N, Fernandez-Cruz L, Ricart MJ, Sabater L, Gilabert R, Astudillo E, Real I (1998) Venous graft thrombosis in clinical pancreas transplantation: options for a rescue treatment. Transpl Proc 30:425–426
Martinenghi S, Dell' Antonio G, Secchi A, Di Carlo V, Pozza G (1997) Cancer arising after pancreas and/or kidney transplantation in a series of 99 diabetic patients. Diabetes Care 20:272–275
Miller GJ et al (1993) Hyperlipidemia and hypercoagulability. Prog Lipid Res 32:61
Friend PJ, Mittal S, Page SL et al (2014) De novo donor-specific HLA antibodies: biomarkers of pancreas transplant failure. Am J Transplant 14:1664–1671
Montenovo M, Vaidya S, Bakthavatsalam R, Halldorson J (2014) Pesudoaneurysm after combined kidney/pancreas transplantation presenting with sentinel bleeding: a case report and review. Ann Transplant 19:317–319
Morelli L, Candio G, Campatelli A, Vistoli F, Chiaro M, Balzano E, Croce C, Moretto C, Signori S, Boggi U, Mosca F (2008) Role of color doppler sonography in

post-transplant surveillance of vascular complications involving pancreatic allografts. J Ultrasound 11:18–21
Morgan T, Harbell J, Stock P et al (2013) Sonographic finding following pancreas transplantation. Transplantation 96(S6):423
Muthusamy AS, Giangrande P, Friend P (2010) Pancreas allograft thrombosis. Transplantation 90:705–707
Nalesnik MA (2001) The diverse pathology of post-transplant lymphoproliferative disorders: the importance of standardized approach. Transpl Infect Dis 3(2):88–96
Nath D, Grussener A, Kandaswamy R et al (2005) Late anastomotic leaks in pancreas transplant recipients: clinical characteristics and predisposing factors. Clin Transplant 19:220–240
Nordin P, Hansson BG, Hansson C, Blohme I, Larko O, Andersson K (2007) Human papilloma virus in skin, mouth and uterine cervix in female renal transplant recipients with or without a history of cutaneous squamous cell carcinoma. Acta Derm Venereol 87:219–222
Otley CC, Cherikh WS, Salasche SJ, McBride MA, Christenson LJ, Kauffmann HM (2005) Skin cancer in organ transplant recipients: effect of pre transplant end-organ disease. J Am Acad Dermatol 53:783–790
Paraskevas S, Coad JE, Gruessner A, Kandaswamy R, Humar A, Sutherland DER, Gruessner RWG (2005) Posttransplant lymphoproliferative disorder in pancreas transplantation: a single-center experience. Transplantation 80:613–622
Parr E, Humar A, Kandaswamy R et al (2000) Prolonged preservation increases surgical complications after pancreas transplants. Surgery 127:545
Petruzzo P, Da Silva M, Feitosa LC, Dawahra M, Lefrancois N, Dubernard JM, Martin X (2000) Simultaneous pancreas-kidney transplantation: portal versus systemic venous drainage of the pancreas allografts. Clin Transplant 14:287–291
Philosophe B, Farney A, Schweitzer E, Colonna J, Jarrell B, Krishnamurthi V, Wiland A, Bartlett S (2001) Superiority of portal venous drainage over systemic venous drainage in pancreas transplantation. A retrospective study. Ann Surg 234(5):689–696
Pirsch JD, Odorico JS, D'Alessandro A, Knechtle SJ, Becker BN, Sollinger HW (1998) Post-transplant infection in enteric versus bladder-drained simultaneous pancreas-kidney transplant recipients. Transplantation 66:1746–1750
Polo JM, Morales JM, Blanco M, Augirre JF, Andres A, Diaz R, Jimenez C, Leiva O, Meneu JC, Moreno E, Pamplona M, Passas J, Rodriguez A, De la Rosa F (2009) Urological complications after simultaneous pancreas-kidney transplantation. Transplant Proc 41:2457–2459
Redfield RR, Scalea J, Odorico J (2015) Simultaneous pancreas and kidney transplantation: current trends and future directions. Cur Opin Organ Transplant 20:94–102
Rigley T, Alonso D, Dunn T et al (2008) Increased pancreatitis in allografts flushed with histidine-tryptophan-ketoglutarate solution: a cautionary tale. Am J Transplant 8:1942–1945
Saad WEA, Darwish WM, Turba UC (2012) Endovascular management of vascular complications in pancreatic transplants. Vasc Endovascular Surg 46:262–268
Schenker P, Vonend O, Ertas N, Wunsch A, Schaeffer M, Rump L, Viebahn R (2009) Incidence of pancreas graft thrombosis using low-molecular weight heparin. Clin Transplant 23:407–414
Schleihner S, Theodorakis J, Illner WD, Leitl F, Abendroth D, Land W (1992) Ulcer perforation in the grafted duodenal segment following pancreatic transplantation – a case report. Transplant Proc 24:827
Sethi PS, Elkhammas EA, Pollifrone DL, Henry ML, Ferguson RM (1995) Pre and Post transplant urologic work up in simultaneous kidney/pancreas transplant: preliminary results of an ongoing study. Transplant Proc 27:3083
Sinha S, Muthusamy A, Vaidya A et al (2009) Pancreas graft thrombosis following intravenous immunoglobulin administration to treat parvovirus B19 infection. Transpl Infect Dis 11:463–466
Sollinger HW, Odorico JS, Knechtle SJ et al (1998) Experience with 500 simultaneous pancreas-kidney transplants. Ann Surg 228:284
Spanogle JP, Kudva YC, Dierkhising RA, Kremers WK, Roenigk RK, Brewer JD, Prieto M, Otley CC (2012) Skin cancer after pancreas transplantation. J Am Acad Dermatol 67:563–569
Stephanian E, Gruessner RW, Brayman KL, Gores P, Dunn DL, Najarian JS (1992) Conversion of exocrine secretions from bladder to enteric drainage in recipients of whole pancreatico-duodenal transplants. Ann Surg 216:663–672
Sutherland DE, Gruessner R, Dunn D, Matas A, Humar A, Kandaswamy R, Mauer M, Kennedy W, Goetz F, Robertson P, Gruessner A, Najarian JS (2001) Lessons learned from more than 1,000 pancreas transplants at a single institute. J Ann Surg 233(4):463–501
Tan M, Di Carlo A, Stein LA et al (2001) Pesudoaneurysm of the superior mesenteric artery after pancreas transplantation treated by endovascular stunting. Transplantation 72(2):336–338
Taylor RJ, Mays SD, Grothe TJ, Stratta RJ (1993) Correlation of preoperative urodynamic findings to postoperative complications following pancreas transplantation. J Urol 150:1185
Taylor AL, Marcus R, Bradley JA (2005) Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol 56:155–167
Troppmann C, Gruessner A, Benedetti E et al (1996) Vascular graft thrombosis after pancreatic transplantation: univariate and multivariate operative and nonoperative risk factor analysis. J Am Coll Surg 182:285–316
Troppmann C, Gruessner AC, Dunn DL, Sutherland DR, Gruessner RW (1998) Surgical complication requiring early relaparotomy after pancreas transplantation. A multivariate risk factor and economic impact analysis of the cyclosporine era. Ann Surg 227(2):255–268

Troppmann C et al (2010) Complications of pancreas transplantation. Curr Opin Organ Transplant 15:112–118

Tzakis A, Carroll P, Gordon R, Yokoyama I, Makowka L (1989) Arterial mycotic aneurysm and rupture: a potential fatal complication of pancreas transplantation in diabetes mellitus. Arch Surg 124(6):660–661

Vaidya A, Muthusamy A, Hadjianastassiou V, Roy D, Elker D, Moustafellos P, Muktadir A, Sinha S, Friend P (2007) Simultaneous pancreas-kidney transplantation: to anti-coagulate or not? Is that a question? Clin Transplant 21:554–557

Venstrom JM, McBride MA, Rother KI et al (2003) Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 290:2817–2823

Verni MP, Leone JP, DeRoover A (2001) Pesudoaneurysm of the Y-graft/iliac artery anastomosis following pancreas transplantation: a case report and review of the literature. Clin Transplant 15:72–76

Verschuuren EA, Bakker NA, Van Imhoff GW et al (2005) HLA antigens and post renal transplant lymphoproliferative disease: HLA-B matching is critical. Transplantation 80:595–599

West M, Stevens RB, Metrakos P, Foshager MC, Jessurun J, Sutherland DER, Gruessner RW (1998) Renal pedicle torsion after simultaneous kidney-pancreas transplantation. J Am Coll Surg 187(1):80–87

Woo EY, Milner R, Brayman KL, Fairman RM (2003) Successful PTA and stenting for acute iliac arterial injury following pancreas transplantation. Am J Transplant 3:85–87

Wullstein C, Woeste G, Zapletal C, Trobisch H, Bechstein WO (2003) Prothrombotic disorders in uremic type-1 diabetics undergoing simultaneous pancreas and kidney transplantation. Transplantation 76(12):1691–1695