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Medical and Surgical Management of the Failed Pancreas Transplant

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Abstract. Despite the continued improvements in pancreas transplant outcomes in recent decades, a subset of recipients experience graft failure and can experience substantial morbidity and mortality. Here, we summarize what is known about the failed pancreas allograft and what factors are important for consideration of retransplantation. The current definition of pancreas allograft failure and its challenges for the transplant community are explored. The impacts of a failed pancreas allograft are presented, including patient survival and resultant morbidities. The signs, symptoms, and medical and surgical management of a failed pancreas allograft are described, whereas the options and consequences of immunosuppression withdrawal are reviewed. Medical and surgical factors necessary for successful retransplant candidacy are detailed with emphasis on how well-selected patients may achieve excellent retransplant outcomes. To achieve substantial medical mitigation and even pancreas retransplantation, patients with a failed pancreas allograft warrant special attention to their residual renal, cardiovascular, and pulmonary function. Future studies of the failed pancreas allograft will require improved reporting of graft failure from transplant centers and continued investigation from experienced centers.

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Survival rates for the simultaneous pancreas and kidney transplant have improved significantly during the past 20 y. Current recipients of simultaneous pancreas and kidney transplants can expect a 5-y pancreas survival of 73% and a 10-y pancreas survival rate of 56%.[1] For those that survive past the first year, the 5-y pancreas survival rates improve from 80% to 84%.[2] Over the past 10 y, the rates of early pancreas graft loss have declined from 11.7% to 6.2% in 2018 to 2019 time period.[3] Despite these improvements, management of a failed pancreas allograft remains a challenge because it carries a significantly increased risk of morbidity and mortality. There is marked heterogeneity in how different programs and providers manage failed pancreas transplants with limited data. Hence, we propose guidance on how best to medically and surgically manage these patients. Our review and recommendations are based on consensus within our Kidney Recipients with Allograft Failure–Transition of Care workgroup using existing data and common practices among experts in this field. We will review the definition of pancreas allograft failure and cover immunosuppression tapering strategies in a failing

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allograft. Complications of pancreas transplant and the management of symptomatic rejection will be discussed. Finally, we will provide guidance on the transition of care after a pancreas allograft has failed and candidacy considerations for a subsequent pancreas transplant. This article is a work product of the American Society of Transplantation's Kidney Pancreas Community of Practice.

MATERIALS AND METHODS

The review article was divided into 9 main topics. Each subtopic was approached and reviewed by 3 to 4 authors. The whole group met monthly in addition to the subgroup meetings. A literature review was then performed, and references were saved in DropBox.

Each subgroup performed a further literature review based on their specific topic. All members participated in monthly teleconferences to share the findings and discuss the key points. Three authors were responsible for merging the work of the 9 groups into 1 file. As transplant centers may have different protocols, a general consensus was taken during the monthly meetings in terms of management guidelines for the article. All meetings were performed virtually. First and senior authors did a thorough review and outline of the topics covered, edited the article, and created the final document.

Defining Pancreas Graft Failure

For many years in the United States, there was no standardized definition for reporting pancreas allograft failure to the Organ Procurement and Transplant Network (OPTN) registry.[4] Individual transplant centers were left to use their clinical judgment to report pancreas graft failures, resulting in variable reporting. This restricted the ability of the Scientific Registry of Transplant Recipients (SRTR) to analyze and compare outcomes across different transplant programs.[5] The last time the SRTR reported >1-y pancreas graft survival was in the 2013 Annual Data Report.[6] Subsequently, the SRTR stopped reporting >90-d pancreas graft survival in their 2014–2019 Annual Data Reports because of the recognition that without a standard definition of graft failure the validity of the data was uncertain, and center-level differences might reflect differences in reporting practices rather than clinically meaningful differences in outcomes.[3,7]

Events generally accepted as reflective of pancreas graft failure include graft pancreatectomy, patient death, or registering for a subsequent pancreas or islet cell transplant.[4,8] Additional functional endpoints—which were historically not incorporated in a formal definition of graft failure—include insulin use, amount of insulin, duration of insulin therapy, C-peptide levels, and hemoglobin A1c values. Examples of different definitions of pancreas graft failure based on these functional parameters include the reinstitution of any insulin therapy, C-peptide <0.4 ng/mL, the reinstitution of up to 50% of the total pre–pancreas transplant insulin requirement, or reinstitution of insulin at 0.5 units/kg/d (Table 1).[9-14] In addition to variable consideration of functional parameters, the duration of insulin use to distinguish temporary graft dysfunction from permanent graft failure was also controversial. The OPTN Pancreas Transplantation Committee performed a multicenter retrospective study to determine if undetectable C-peptide levels correspond to center-reported graft failures. The study showed that graft failure was being reported at all levels of C-peptide values. Similarly, returning to insulin use was reported at all levels of C-peptide values (Table 2).[10] The study concluded that centers declare graft failure at varying levels of C-peptide and do not consistently report C-peptide data.[10]

TABLE 1.

Historical proposals for defining pancreas allograft failure

- Reinstitution of any insulin therapy
- Reinstitution of up to 50% of the total pre–pancreas transplant insulin requirement
- Reinstitution of insulin at 0.5 units/kg/d
- C-peptide ≤0.4 ng/mL
- Hemoglobin A1c ≥7%
- Graft pancreatectomy
- Registering for a subsequent pancreas transplant or islet cell transplant
- Patient death

In 2015, the OPTN Board of Directors approved a standard definition for pancreas graft failure.[5] The definition mandates that US transplant programs report pancreas graft failure when any 1 of the following occurs[15]:

1. A recipient's transplant pancreas is removed.
2. A recipient reregisters for a pancreas transplant.
3. A recipient registers for an islet transplant after receiving a pancreas transplant.
4. A recipient's total insulin use is ≥0.5 units/kg/d for 90 consecutive days.
5. A recipient dies.

Due to programming requirements, this policy was not implemented until February 28, 2018.[16]

The OPTN/SRTR Annual Data Report 2020 marks the first year that the new standard definition for pancreas graft failure has been in effect for an entire year.[17] Despite this achievement, concerns remain about incomplete data reporting. The OPTN Pancreas Transplantation Committee noted that insulin duration or dosage was not always reported by transplant centers and that pancreas grafts that met the criterion of ≥0.5 unit of insulin/kg/d for 3 mo were not always marked as failed.[16] Despite the implementation of a standard definition for pancreas graft failure, obstacles to data reporting still need to be addressed to accurately forecast pancreas graft survival.

Patient Survival and Morbidity After Pancreas Graft Failure

A higher mortality has been reported with a failed pancreas transplant. In an analysis of SRTR data of SPK waitlisted patients with type 1 diabetes transplanted from 1997 to 2005, patients with a failed pancreas transplant have a 64% higher risk of kidney graft failure and 166% higher risk of patient death compared with SPK recipients with a functional pancreas at 1 y.[18] Similar findings were reported in patients with type 2 diabetes who received a SPK between 2000 and 2016. SPK recipients with a failed pancreas at 3 mo of transplant had 3 times higher risk of patient death compared with recipients with a functional pancreas.[19]

An analysis of the International Pancreas Transplant Registry and United Network for Organ Sharing database from 2001 to 2016 showed lower 3-y patient survival in SPK recipients with a failed pancreas versus a functioning pancreas allograft.[20] In a multivariate analysis of patient survival,

TABLE 2.

Distribution of C-peptide values in cases with pancreas graft failure

	N	Mean	Min	25th percentile	Median	75th percentile	Max
Pretransplant C-peptide, ng/mL	149	2.03	0	0.1	0.2	0.5	33
C-peptide at return to insulin, ng/mL	94	2.28	0.1	0.6	1.46	3.4	12.1
C-peptide at graft failure, ng/mL	233	2.11	0	0.4	0.9	2.7	33

Data from Niederhaus et al[10] showed graft failure being reported at different levels of C-peptide values.

the most significant factor was graft failure in all 3 pancreas allograft categories—SPK, pancreas transplant alone (PTA), and pancreas after kidney transplant (PAK). In SPK, a failed kidney graft resulted in a relative risk of death of 10.38 and a failed pancreas of 2.56, demonstrating the importance of both functioning kidney and pancreas grafts. In PTA and PAK, the impact of a failed pancreas graft also increased risk of mortality—PTA relative risk of 3.65 and PAK relative risk of 2.15.[20]

In most SPK, the pancreas allograft fails before the kidney graft. In an International Pancreas Transplant Registry analysis of 9428 primary SPK transplants performed between 2000 and 2010, the subsequent function of the kidney was related to the reason for pancreas graft failure. Early pancreas failure for technical reasons, especially graft thrombosis, was associated with a 3-y kidney graft survival of 81%. Pancreas failure due to infection or immunological reasons was associated with a 3-y kidney graft survival of only 68%.[21]

A word of caution for SPK recipients with a failed renal allograft. As patients resume dialysis, the follow-up with the transplant center may become less frequent. As a result, immunosuppression may not be monitored closely, minimized, or even stopped inadvertently, leading to pancreas allograft rejection. Therefore, we recommend paying special attention to this situation to avoid a preventable rejection.

A pancreas allograft, whether failing, maybe a source of significant morbidity (related to thrombosis, if it occurs), such as infection of necrotic tissue, enteric leak, bowel obstructions, and bleeding.[22] The enteric complications can be significant, occurring in up to 20% of pancreas transplant recipients.[23] The most common bowel complications are anastomotic leaks and small-bowel obstruction.[23] Although rare, arterioenteric fistulas are a potentially life-threatening complication, so it is crucial for patients to immediately report any gastrointestinal bleeding. Details on management of these complications are discussed in the section Surgical Management of the Failed/Failing Pancreas Graft.

Management of the Failed/Failing Pancreas Graft

Investigation of the Failed/Failing Pancreas Graft

The initial investigation of a failing pancreas allograft is usually initiated after finding an abnormally elevated blood glucose level. Chronically elevated glucose levels may be confirmed with an elevated hemoglobin A1c level. A low C-peptide level of ≤0.4 ng/mL suggests pancreatic graft beta cell dysfunction, but it does not rule out concurrent insulin resistance. These test findings may occur late in the course of pancreas graft failure, so more sensitive measures of glucose homeostasis may need to be used, such as the oral glucose tolerance test and the mixed meal tolerance test. The oral glucose tolerance test is recognized as the gold standard for diagnosing beta cell dysfunction; however, it does not replicate the process of absorption and digestion of complex foods. The mixed meal tolerance test is physiologically more tolerable because it has more similarities to common dietary patterns.[24] These tests help describe the state of pancreas graft dysfunction but, unfortunately, do not provide much detail into why a graft may be failing.

Elevated pancreatic enzyme levels (serum amylase and lipase) are associated with exocrine parenchymal injury or inflammation and are commonly seen with acute pancreas graft rejection. However, these findings are not specific and may also be seen with infection or other nonimmunological-related pancreas transplant complications. Additionally, elevated pancreatic enzymes can arise from the native pancreas or elevated amylase from salivary glands, so these should be investigated if no transplant issue is found. In bladder-drained pancreases, a decrease in urinary amylase is suggestive of graft failure, but bladder-drained pancreas transplants have become more of the exception instead of the norm. Donor-specific antibodies are associated with antibody-mediated rejection, and we recommend including them in the workup of pancreas graft rejection and failure. In SPK recipients, a rising serum creatinine could be a sign of pancreas graft rejection because there is a 60% concordance of pancreas and kidney rejection.[25] However, we recommend further investigation because the concordance rate is far from ideal.

Declining pancreas graft function in the setting of normal pancreatic enzyme levels may be seen with excessive weight gain, drug-induced new-onset diabetes after transplant, or recurrence of autoimmune type 1 diabetes. After excessive weight gain, measures to promote healthy weight loss should be implemented and include exercise and nutritional counseling. Some immunosuppression regimens that include tacrolimus and steroids can be diabetogenic, so alternative regimens that minimize or eliminate these agents could be considered. In patients with type 1 diabetes who received a pancreas transplant, recurrence of autoimmune diabetes has been described and can be screened for by testing for circulating autoantibodies to islet cell autoantigens, such as anti–glutamic acid decarboxylase, anti–tyrosine phosphatase, anti-insulin antibodies, islet cell antibodies, and anti–cation efflux transporter ZnT8 antibodies.[26]

Other diagnostic tests include radiological imaging such as ultrasound and computed tomography, which may show a peritransplant fluid collection, pancreatic phlegmon, pseudocyst, or allograft swelling. A pancreas transplant biopsy is a gold standard for diagnosing rejection, but biopsying the pancreas may not always be feasible because of the graft's location or surgical risk. In SPK recipients, a kidney allograft biopsy can be considered when a pancreas allograft biopsy is not considered safe to perform.[25] However, as mentioned previously, the concordance of pancreas and kidney rejection is not ideal, so, in our opinion, extrapolating kidney allograft biopsy results to the pancreas allograft needs to be interpreted very cautiously.

Emerging technologies in the evaluation of pancreas graft failure include plasma donor-derived cell-free DNA. This emerging biomarker for alloimmune activity has already been approved in kidney transplant recipients and is currently being studied as a possible future tool for assessing rejection in simultaneous pancreas-kidney transplant recipients.[27]

Optimizing Glycemic Control

Hyperglycemia after pancreas transplant is a critical medical condition that needs immediate attention. It is crucial to distinguish recurrent or de novo type 1 or type 2 diabetes from pancreas allograft rejection by the measures described above. Glycemic control in the posttransplant period, especially in the setting of failing/failed pancreas allograft, is key to preventing other long-term morbidities such as cardiovascular complications. Insulin remains the main stay of glycemic control after a failing/failed pancreas allograft. Although emerging data showed the cardiovascular and metabolic benefit of dipeptidyl pepridase-4 inhibitors, glucagon-like peptide-1 agonists, and sodium-glucose transport protein 2 inhibitors in non–pancreas transplant patients, the data in pancreas transplant patients are limited.[28-30]

Signs, Symptoms, and Medical Management of Symptomatic Rejection in a Failed Pancreas Graft

Identifying rejection, even in a functioning pancreas allograft, can be challenging because most rejections are clinically asymptomatic. Pancreas allograft function is commonly monitored by several parameters, including serum amylase, serum lipase, blood sugar level, C-peptide level, hemoglobin A1c, or if bladder drained, urinary amylase.[31] However, as mentioned earlier, these are nonspecific markers because other potential causes can exist for these laboratory values to be abnormal.[31] Although elevated pancreatic enzymes are more prevalent in acute rejection, it is not uncommon for patients to develop chronic rejection and graft failure without a significant rise in their serum enzymes.[31] Among SPK recipients, serum creatinine is not always a reliable indicator of pancreatic graft rejection[32] because discordance in the rate and types of rejection among simultaneous biopsies of both allografts among SPK recipients can be seen.[33]

As most pancreas transplants occur in the form of SPK or PAK, patients with failed isolated pancreas allografts are usually maintained on immunosuppression for the functional kidney transplant. As a result, many patients with failed pancreas allografts are asymptomatic. In one study, among 889 SPK and 133 PAK recipients who developed 246 isolated late pancreas allograft failures (>3 mo posttransplant), only 50 patients required pancreatectomy.[34] Of those 50 allograft pancreatectomies, 39 were performed because of various signs and symptoms, including abdominal pain (18 patients), fever (9 patients), sepsis/septic shock (4 patients), hyperglycemia/diabetic ketoacidosis (5 patients), gastrointestinal/genitourinary bleed (6 patients), and severe nausea/vomiting (6 patients). In another study, among all forms of pancreas transplant (SPK, PAK, and PTA), 31 had late (>14 d) pancreas graft loss, of whom 19 underwent allograft pancreatectomy.[35] Of those late graft pancreatectomies, 13 presented with abdominal pain and/or nausea, 3 presented with vascular issues (2 arterioenteric fistulae and 1 pseudoaneurysm), and the remaining 3 underwent pancreatectomy at the time of pancreas retransplant.

Most of the existing literature detailing failed allograft management is in the field of kidney transplantation. Kidney transplant recipients with a failed kidney allograft may present with graft intolerance syndrome that is clinically manifested by fever, malaise, local pain, gross hematuria, and/or graft tenderness after discontinuation of the immunosuppressive medications.[36,37] Multiple studies have explored the various surgical and medical management options for kidney graft intolerance, including embolization of the graft, surgical nephrectomy, continuation, or bolus of immunosuppression.[37-39] To our best knowledge, no studies have explored options for the management of failed pancreas transplants. The role of high-dose steroids in patients with symptomatic failed pancreas allografts is unclear. Caution must be made, particularly for patients who may have an underlying infection. For example, in the case of patients with failed kidney allografts, surgical intervention may ultimately be warranted to address symptoms.

To summarize, many patients with failed pancreas transplants are asymptomatic; however, some may present with symptoms, mainly abdominal pain, despite being on immunosuppressive medications. Providers should have a low threshold to investigate with appropriate history, physical examination, laboratory, and imaging studies. Patients with a symptomatic failed pancreas transplant may ultimately require an allograft pancreatectomy.

Surgical Management of the Failed/Failing Pancreas Graft

After pancreas transplantation, several immediate problems may occur that necessitate acute intervention. Early thrombosis diagnosed by ultrasound or suspected clinically requires rapid operative reexploration. If the graft appears viable, systemic heparinization is appropriate and thrombectomy can be attempted. Graft thrombosis or necrosis necessitates transplant pancreatectomy (Figure 1), with concurrent management of any sequelae such as enteric leakage, shock, or abdominal sepsis. Early and late pseudoaneurysms involving the arterial Y-graft or other pancreatic arterial vasculature are particularly insidious, can present dramatically, and require urgent operative or interventional radiology management. When considering surgical options, we recommend that the surgical approach be specific to the acuity and likelihood of allograft salvage.

The arterioenteric fistula is a rare but potentially catastrophic vascular complication of a failed pancreas transplant after immunosuppression withdrawal. In a single-center study from Indiana University, 5 cases of arterioenteric fistula (incidence 1.4%) started with a sentinel bleed and then progressed to massive gastrointestinal bleeding. Four of these patients had a failed allograft, of which 3 occurred in the setting of cessation of immunosuppression.[40] In a more recent retrospective study from the University of Minnesota, 10 cases of arterioenteric fistulas were reported (incidence <0.5%), of whom 7 occurred in the setting of a failed pancreas transplant. Eight of 10 patients required transplant pancreatectomy for definitive treatment. One patient died of rebleeding.[41] Although not well understood, the cause of an arterioenteric fistula might be mediated by chronic pancreas allograft rejection.[40] Due to its serious nature, we strongly stress that patients immediately report any gastrointestinal bleeding.

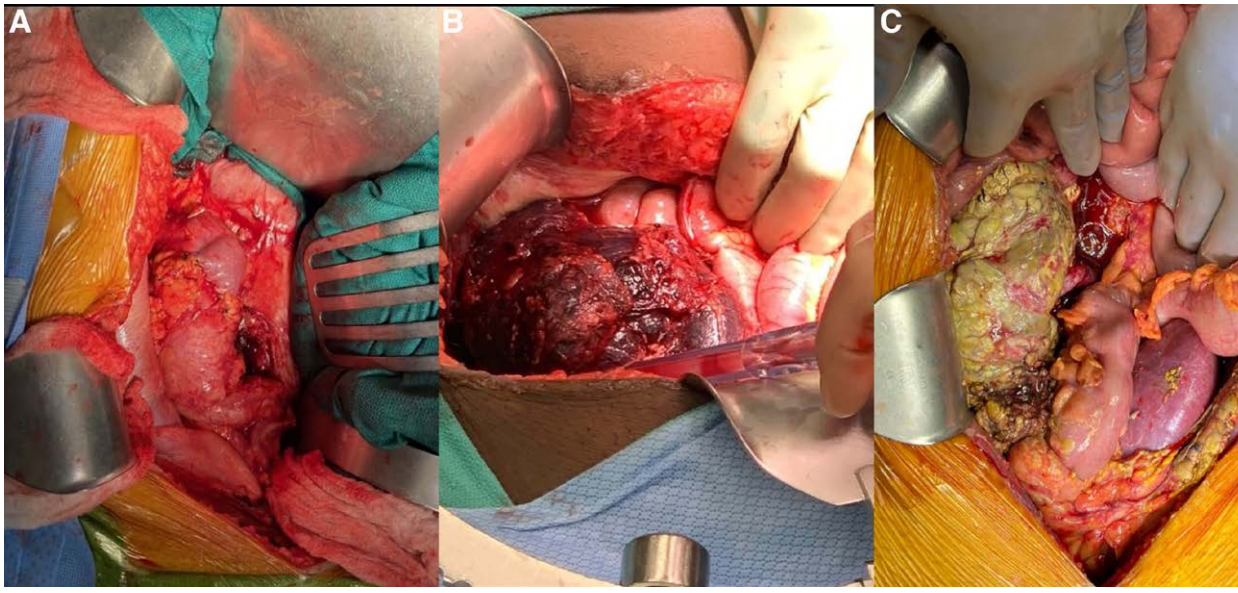

FIGURE 1. A, A healthy-appearing transplanted pancreas after reperfusion. B and C, Necrotic pancreata showing at operative reexploration, both managed by allograft pancreatectomy with restoration of intestinal continuity.

Other complications after pancreas transplantation may have a more protracted or even chronic presentation, such as enteric leaks, bowel obstruction, or persistent fluid collections.[22,23] Pancreas allografts can be salvaged after a complication with the enteric leak by conversion to a Roux-en-Y enteric configuration or, if anatomically possible, conversion to bladder drainage. Small-bowel obstructions are usually managed conservatively, but surgeons should have a low threshold to operate, given the possibility of adhesions and internal hernias that may not present with significant abdominal distension.[23] Fluid collections are often managed with percutaneous drains, placed either operatively or under radiographic guidance, and antibiotics. If certain complications, such as enteric leaks and fluid collections, persist for a prolonged period, especially if accompanied by immunosuppressive side effects or graft dysfunction, it is our opinion that the pancreas should be removed. Chronic rejection in the setting of a functioning kidney transplant may increase the chances of concomitant or subsequent rejection of the transplanted kidney. Hence, graft pancreatectomy might be considered to increase the survivability of the kidney allograft. Other indications for pancreatectomy include arterial fistula and chronic pain that is associated with pancreas rejection. Retransplant outcomes have improved, but medical treatment options for diabetes have also significantly improved (including longer-acting insulins, oral agents such as sodium-glucose cotransporter-2 inhibitors, and improved insulin pumps with feedback mechanisms). Hence, a final decision on which patients would most benefit from retransplantation versus ongoing medical therapy should be made by experienced transplant teams, with clear counseling of patients on the pros and cons of either path.

Removal of a failed allograft before retransplant, if not otherwise causing problems, is generally avoided. If not done early after transplant, transplant pancreatectomy can be a treacherous operation due to the need for vascular control, the risk of distal limb ischemia, and the challenge of restoring enteric continuity. If not in a situation where rapid vascular control is required, the enteric anastomosis is often resected first to allow better visualization of the vasculature. Although full proximal and distal control of the native vessels may be required, it is often possible to simply obtain vascular control of the transplanted portal vein and Y-graft. The transplanted pancreas is removed, and bowel continuity is restored unless a planned reoperation in 24 to 48 h is required if there has been an extensive enteric leak. Preoperative arterial embolization or even placement of a covered arterial stent, similar to that of transplant nephrectomy, may play a role in avoiding excessive blood loss, particularly for difficult pseudoaneurysms. Additionally, there are other causes of pancreatic symptoms, damage, or failure, including traditional causes of pancreatitis such as alcohol, resulting in pancreatic necrosis or pseudocyst, malignant masses, or inflammation from nearby disease processes, such as acute appendicitis, diverticulitis or phlegmon, that may require operative intervention (Table 3). As stressed previously, gastrointestinal or sentinel bleeding may indicate a potentially catastrophic and life-threatening vascular complication, so it is imperative for patients to report this immediately to their transplant team.

Immunosuppression Withdrawal in a Failed Pancreas Graft

Although survival rates of pancreas transplant continue to improve,[1-3] the management of immunosuppression in the setting of pancreas graft failure has not been well studied or described. The most common immunosuppression protocol in an adult pancreas transplant recipient is induction with an antibody-depleting agent (ie, antithymocyte globulin or alemtuzumab) combined with a maintenance regimen of a calcineurin inhibitor (CNI) and an antimetabolite with or without steroids. There are several reasons for tapering immunosuppression after graft failure, which include infectious, neoplastic, and metabolic side effects.[42,43] However, we believe that this needs to be balanced with the potential risks for allosensitization, graft pain, or necrosis from an acutely rejecting allograft. In a study of kidney transplant patients with a failed allograft, weaning of immunosuppression led to a 14-fold

TABLE 3.

Surgical management of the failing/failed pancreas allograft

Diagnosis	Treatment options
Thrombosis: central or peripheral, partial or complete • Venous: portal, superior mesenteric, splenic • Arterial: iliac (± associated leg ischemia), Y-graft (either arm or both)	Systemic heparinization, thrombectomy ± transplant pancreatectomy
Intra-abdominal Hemorrhage • Anastomotic bleed: arterial (iliac or within the Y-graft), venous, or both • Pseudoaneurysm: iliac or Y-graft	Volume resuscitation with blood products; factors Proximal and distal control and hemostasis ± preoperative embolization or covered arterial stent ± transplant pancreatectomy
Pancreatic necrosis	Transplant pancreatectomy
Enteric leak	Simple repair Roux-en-Y creation Bladder drainage Bowel continuity when possible ± damage control, staged closure
Persistent fluid collections	Percutaneous drains, antibiotics, surgical washout Consider pancreatectomy
Pancreatitis, pancreatic pseudocyst	Source control, necrosectomy, cyst-enterostomy ± transplant pancreatectomy
Adjacent phlegmon	Resection of offending organ, eg, appendectomy ± transplant pancreatectomy
Chronic rejection with chronic pain	Transplant pancreatectomy
Arterial fistula	Endovascular intervention (embolization, stent) Transplant pancreatectomy
Malignancy	Observation Enucleation of mass Traditional oncological resection ± transplant pancreatectomy

higher risk of allosensitization, but infections were higher in patients in whom immunosuppression was continued.[44]

As of June 2020, the number of US pancreas transplant recipients alive was closing in on 20 000.[17] It is imperative that providers have a rational way of handling immunosuppression with a failed pancreas graft. Therefore, we propose a strategy for weaning immunosuppression for a failed pancreas transplant (Figure 2). When considering immunosuppression withdrawal after pancreas graft failure, it is important to consider whether this is occurring in the context of a PTA or dual pancreas-kidney transplants (SPK or PAK). For dual pancreas-kidney transplant recipients, if the pancreas graft has failed, but the kidney graft function remains intact, then immunosuppression should continue at the recommended targets for optimal kidney allograft function. However, if both allografts have failed, then immunosuppression weaning can proceed.

Another important consideration for immunosuppression management is the cause of pancreas graft failure. If infection or malignancy is the primary reason for graft loss, we believe a more rapid immunosuppression taper should be considered. We recommend stopping the antimetabolite and tapering off the calcineurin inhibitor (CNI) with or without steroids for 3 mo. Likewise, if the pancreas graft fails due to thrombosis or other surgical causes, a rapid withdrawal of immunosuppression—similar to the infection/malignancy taper outlined previously—should be considered with potential graft pancreatectomy at the discretion of the surgical team. When rejection is the cause of pancreas graft failure, it is our opinion that a somewhat slower taper of immunosuppression should be considered to reduce the potential for an increased inflammatory response in the graft. Our recommendation is to reduce or taper the antimetabolite during the first 3 mo but continue the CNI with or without steroids for at least 6 mo. Immunosuppression management after 6 mo will depend on other factors such as renal function and retransplant potential.

In certain patients like those who have some degree of graft or native kidney dysfunction or dialysis patients who wish to maintain residual renal output, a renal sparing strategy may need to be pursued. This strategy would require stopping the CNI (and associated nephrotoxicity) while maintaining a lower dose of antimetabolite with or without steroids. If a renal-sparing strategy is not required, then we recommend stopping the antimetabolite but maintaining a lowered dose of CNI with or without steroids (Figure 2).

In patients who are not candidates for retransplantation, we recommend tapering all remaining immunosuppression off for 3 mo. However, for retransplant candidates, we believe that a low level of immunosuppression can be maintained to avoid further allosensitization while minimizing immunosuppression-related complications. There are no data on the optimal duration of maintenance immunosuppression after pancreas graft failure, but there is some literature on immunosuppression management after kidney graft failure that suggests that maintenance immunosuppression to prevent allosensitization can be considered for up to 12 mo after graft failure.[37,45] Because there is no evidence-based practice for immunosuppressive management after pancreas graft failure, we propose future directions and areas for future research in Table 4.

Preparing the Patient for a Second Pancreas Transplant

Repeat pancreas transplantation is not common but may be offered at experienced transplant centers. The

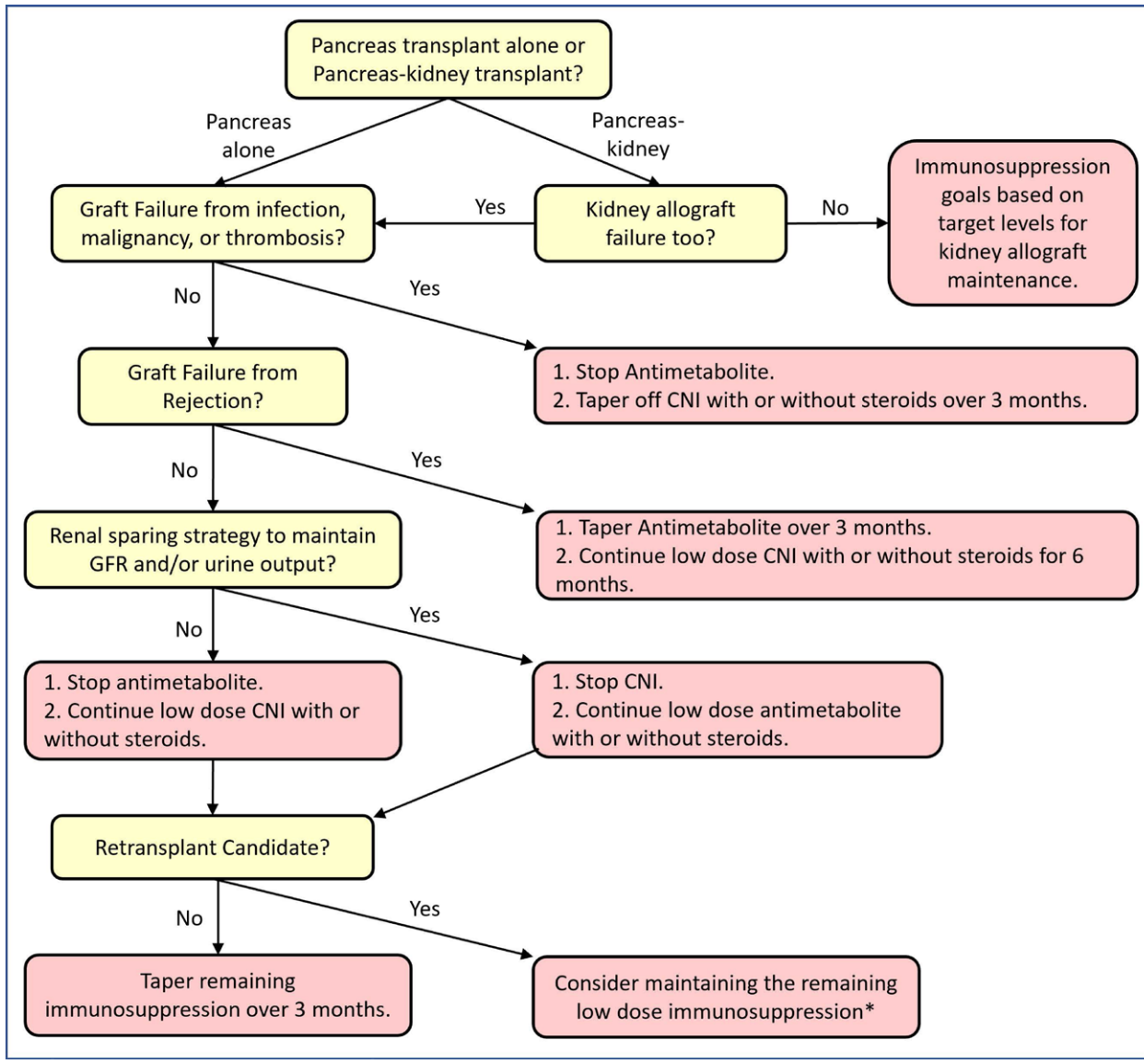

FIGURE 2. Proposed strategy for weaning immunosuppressive medications for a failed pancreas transplant. A yellow box indicates a decision point and a red box indicates an action process. *Based on immunological risks and adverse drug events. CNI, calcineurin inhibitor; GFR, glomerular filtration rate.

first pancreas retransplant was performed in 1978 at the University of Colorado but failed in 2 wk from rejection because immunosuppression options were limited at that time compared with today.[46] Since then, retransplant outcomes have improved, but, on the other hand, medical treatment options for diabetes have also significantly improved (including longer-acting insulins, oral agents such as sodium-glucose cotransporter-2 inhibitors, and improved insulin pumps with feedback mechanisms).[47] Hence, a final decision on which patients would most benefit from retransplantation versus ongoing medical therapy should be made by experienced transplant teams, with clear counseling of patients on the pros and cons of either path. Patients should also be counseled that medical treatment options are much further advanced, and a final decision on which patients would most benefit from retransplantation versus ongoing medical therapy should be made by experienced transplant teams.

Indications for a Repeat Pancreas Transplant

Compared with the candidacy for the first pancreas transplant, the indications for pancreas retransplantation must be considered more judiciously for several reasons. First, pancreas retransplant candidates are surgically more complex because of the prior allograft and all of its potential surgical complications. Second, the cumulative burden of immunosuppression needs to be thoughtfully weighed because of the long-term risk of infection and malignancy. Finally, cardiovascular risk needs careful assessment in retransplant candidates who carry just as many, if not more, comorbidities than at the time of their first transplant.

The medical indications for pancreas retransplant include hypoglycemia unawareness, brittle diabetes, and surgical pancreatectomy. Patients with a failed pancreas as a PTA with worsening kidney function could be considered as a candidate for a subsequent pancreas transplant in a setting of SPK. We think that a glomerular filtration rate of <40 mL/min at

TABLE 4.

Take home points and suggested areas for future research

Take home points	Areas for future research/study
Four main factors determining immunosuppressive medication management with a failing pancreas allograft are: • Cause of pancreas graft failure • Potential unacceptable complications from overimmunosuppression • Renal sparing • Candidacy for subsequent solid organ transplantation	• Identify the clinical outcomes including survival benefits and risks of continued immunosuppressive medications during and after failing pancreas allograft
Best practice for tapering immunosuppressive medications is unknown. The goal of immunosuppressive medication management is to minimize potential complications from overimmunosuppression and chronic CNI nephrotoxicity but still prevent immune reactivation	• Determine appropriate durations of tapering immunosuppressive medications to prevent sensitization and preserve kidney function • Identify risk factors of developing complications from continuing immunosuppressive medications. • Identify a natural course of anti-HLA antibody during and after failing allograft as well as its outcomes related to transplant access and outcomes of retransplantation
Care coordination between the transplant team and endocrinologists is crucial for referral for retransplantation and glycemic control	• Identify factors that affect care collaboration between the transplant team and endocrinologists during and after failing pancreas allograft

CKD, chronic kidney disease; CNI, calcineurin inhibitor.

the time of evaluation could be considered for SPK. However, there are some important issues to consider. For instance, for SPK or PAK retransplants, hypoglycemia unawareness may not be present while there is residual allograft function. The risk of the pancreas retransplant relates more to the perioperative cardiac or surgical risks than to the risk of progression of diabetic complications.

Medical and Surgical Evaluation for a Repeat Pancreas Transplant:

The selection of retransplant candidates based on medical comorbidities, surgical risks, and functional status is crucial. Patients with a failed pancreas allograft tend to be older and often have more medical comorbidity compared with when they received their first transplant. However, carefully chosen pancreas retransplant candidates can still have successful retransplant outcomes. In a series of 52 pancreas retransplant patients with a median age 31 y and median body mass index 23 kg/m^2, Gasteiger et al[48] reported similar allograft survival compared with primary pancreas transplantation. These outcomes may not be applicable to more marginal retransplant candidates.

Appropriate timing for pancreas retransplants is not well described. Allograft failure can occur immediately after the surgery, so it may be preferred to retransplant right after failure to avoid intra-abdominal adhesion and repeat induction immunosuppression.[49] The cause of initial allograft loss is also important because intra-abdominal infection is associated with a high rate of allograft loss after retransplantation.[50] Contraindications to pancreas retransplant are the same as primary transplant. These include severe cardiopulmonary or vascular disease, active infections or malignancy, comorbidities (morbid obesity, substance abuse, advanced liver, or lung disease), and psychosocial instability.

A potential candidate for pancreas retransplantation should undergo a standard transplant evaluation that includes a cardiovascular and pulmonary risk assessment.[51] Kidney function is also an important consideration. Generally, an estimated glomerular filtration rate >40 mL/min is required for pancreas-alone retransplantation, and if it is lower, SPK might need to be considered. Excellent compliance during the first pancreas transplantation is a further selection criterion. Nonadherence to medications has been associated with poor outcomes. Other components of pretransplant evaluation include vascular evaluation (as described below), hypercoagulable workup, cancer screening, infectious disease evaluation, psychosocial evaluation, and functional status assessment.

Evaluation of surgical candidacy begins with determining the transplant needed: either pancreas alone or a pancreas-kidney transplant, depending on kidney function, as noted previously. Having adequate space, as well as both arterial inflow and venous outflow options without problematic atherosclerosis, greatly affects the feasibility of pancreas retransplant. Assessment of the aorta and both iliac systems as options for inflow, evaluation of the vena cava, both iliac systems, and the portal vein as the venous drainage is critical.

Some components of the patient history weigh heavily in the surgical evaluation. Fully understanding the reason for the first graft failure, both in terms of surgical and immunologic complications, can aid in devising a successful approach for retransplantation. For example, there may be vascular abnormalities that contributed to the graft's failure or have developed since the first transplant. Compared with a kidney, the pancreas is a low-flow organ at baseline. As such, patients with uncorrectable chronic hypotension are at increased risk of allograft thrombosis, which may negatively impact candidacy for pancreas retransplantation.

Immunological Considerations for Retransplantation

Similar to kidney retransplantation, pancreas retransplant candidates may have more alloimmune sensitization.[52-54] Fridell et al reported 20 cases of late (>1 mo after the first transplant) pancreas retransplantation. Sixty-five percent of cases had detectable anti-HLA antibody and 25% of cases had a PRA >20%.[54] A highly sensitized state can make retransplantation less likely, even compared with similarly sensitized kidney-only retransplant patients, as centers are often more reluctant to cross donor-specific antigens for a pancreas compared with a kidney.

The majority of pancreas transplants, particularly pancreas retransplants, receive induction with an antibody-depleting agent, such as rabbit antithymocyte globulin or

alemtuzumab.[55-57] The additional use of rituximab with a T cell–depleting agent has been reported to have some success as well.[58] Repeat induction with alemtuzumab may be associated with increased fungal infections.[59] Use of nondepleting induction has been reported as well.[52,60,61] Induction therapy may allow weaning of steroids, although this is less likely in pancreas retransplanation.[52,61]

We recommend the use of T cell–depleting agents for a second pancreas transplant. We favor the use of antithymocyte globulin over the use of alemtuzumab in the setting of subsequent pancreas transplant. In terms of immunosuppression, we recommend keeping tacrolimus in the higher range (such as a trough of 8–12 ng/dL) in the first year of pancreas transplantation.

Donor Considerations

Given the challenges associated with pancreas retransplantation, the donor evaluation is also more focused on the overall compatibility and quality to minimize the factors associated with pancreas allograft failure. Perhaps even more important for a repeat pancreas transplant is the quality of the pancreas itself. Donor pancreata with profound hypotension resulting in ischemic damage may experience significant pancreatitis postreperfusion and are often avoided. Likewise, most surgeons consider substantial fibrosis or fat infiltration not transplantable, whereas some degree of edema may be considered acceptable (**Figure 3**). Every effort should be made to avoid prolonged cold ischemia time because of organ transport or other logistic challenges.[62] As in a primary pancreas transplant, the procurement surgeon should provide an adequate iliac conduit for the Y-graft reconstruction, sufficient iliac vein should a venous extension graft become necessary, and when feasible, additional arterial and venous conduit should creative reconstruction be required. In terms of immunologic matching, limiting both donor-specific antibodies and optimizing HLA matches is helpful. We think that having an actual crossmatch before the surgery is needed as these patients tend to develop more antibodies than the timing before the initial pancreas transplant.

Surgical Considerations of the Retransplant Candidate

Technical aspects are considerable and include prior vascular dissections, atherosclerotic disease, and the location of the failed pancreas (and possibly kidney).[63] The placement options for the new graft may be limited by any of these factors. A careful review of prior operative records and cross-sectional imaging is imperative, both in terms of prior vascular anastomoses and the method of enteric drainage used.

Identifying a suitable location for the arterial inflow can be challenging in the setting of multiple prior transplanted organs. Higher aortic and inferior vena cava vascular targets can be used when needed. Removal of a nonfunctioning kidney transplant or the prior pancreas transplant may be necessary to make vessels, if not thrombosed, available for anastomosis.[64] Atypical arterial extension grafts may also be needed to reach nondiseased vessels.

Venous outflow location can be challenging, as reexploring an already-dissected inferior vena cava or iliac vein can be dangerous with a failed systemically drained pancreas. If the iliac veins are challenging, anastomosis more cephalad on the inferior vena cava is an option, paired with either the proximal iliac artery or aortic inflow. Venous portal drainage may be considered as well. For retransplant in the setting of prior portal drainage, using systemic drainage is a possibility, but retransplant of a graft that was drained via the portal vein again has been successfully reported.[65] Venous extension grafts may also be useful to reach more separated anastomotic sites, although particular care should be exercised to avoid venous kinking, as pancreata with outflow issues are prone to thrombosis. Additional consideration is needed as to whether any prior thigh grafts exist or venous graft stents were placed for a prior use of hemodialysis.

Enteric drainage depends on the orientation of the graft and the configuration of the small intestine. A primary anastomosis to the intestine is often chosen, but this depends on the length of the mesentery and availability of the proximal small intestine. Less commonly, some surgeons favor either the use of a Roux-en-Y enteric limb or bladder drainage to minimize the possibility of enteric leak. Postoperatively, the use of Jackson-Pratt drains and/or nasogastric tubes varies by institutional protocol and sometimes by surgeon. Similarly, postoperative anticoagulation after repeat pancreas transplant is not uniformly described, but many provide a subtherapeutic heparin infusion or early prophylactic subcutaneous heparin for a brief period before starting an aspirin and resuming normal inpatient subcutaneous heparin.

CONCLUSION

Pancreas graft failure is difficult to recognize initially because patients are often asymptomatic, and once confirmed, it is associated with worse patient survival than patients with sustained graft function. Management of

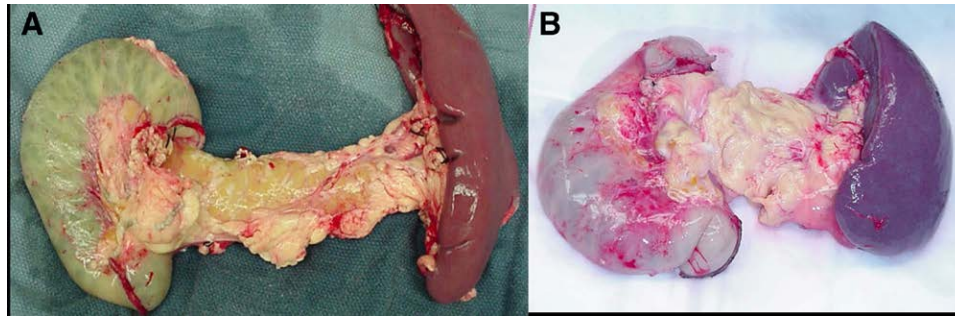

FIGURE 3. A, A safely recovered pancreas with acceptable edema and fat content. B, A fatty pancreas that is not suitable for a primary or repeat pancreas transplant candidate.

the failed pancreas allograft requires careful attention to residual renal function and other preexisting comorbid conditions. Immunosuppression is usually reduced to limit any ongoing infectious and neoplastic morbidities, but this decision must be balanced against the risk of alloimmune sensitization and graft-related complications, which can necessitate graft pancreatectomy. Pancreas retransplant is more complex than the primary transplant and should be considered in patients who have preserved cardiopulmonary reserve. The donor pancreas ideally has a minimal ischemic injury, and the recipient may require resection of existing grafts and have a permissible calcific atherosclerotic vascular disease with patent venous outflow. Similar outcomes to primary pancreas transplant recipients have been shown after pancreas retransplantation at experienced centers in a well-selected patient population. Improvements in the care of the failing allograft will necessitate better reporting of graft failure from transplant centers and ongoing study at experienced centers that more frequently perform pancreas retransplant.

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