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MINIREVIEWS

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ABOUT COVER

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MINIREVIEWS

Donor risk factors in pancreas transplantation

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Abstract

The aim of the work was to analyze and expose the donor and recipient risk factors in pancreas transplantation. In the following paper, we exposed the 2018 Spanish Consensus Document on Donor and Recipient Selection Criteria for Pancreas Transplantation. An assessment of the previous Selection Criteria for Donors and Recipients of Pancreas Transplantation, published in 2005 by the Spanish Pancreas Transplant Group (GETP) and the National Transplant Organization (ONT) was performed. A literature review was performed using Cochrane Library, PubMed and Google Scholar databases. Some of the following terms were used for the literature search: "Diabetes Mellitus," "Pancreas Transplantation," "Insulin-Secreting Cells," "Pancreas Allograft Thrombosis," "Allograft Pancreatitis," "Donors' Risk Factors," "Recipients' Risk Factors," "Pancreas Allograft Rejection" and "Pancreas Allograft Survival." After an extended search, different inclusion criteria were established. Articles and documents with abstracts of full text and in English or Spanish language were selected. Subsequently, different scientific meetings took place during 2015 and 2016 by the GETP. Finally, the updated criteria were published by the GETP and ONT in 2018. Several risk factors have been described in pancreas transplantation that can be divided into donor risk factors: Advanced age (> 50 years); high body mass index (BMI) (> 30 kg/m^2); cause of death (*e.g.*, stroke); previous hyperglycemia; hyperamylasemia; cold ischemia time (greater than 8 or 12 h, depending on the type of donation); the use of vasopressors in the intensive care unit or cardiac arrest; and the macroscopic aspect of the pancreas allograft. The following are recipient risk factors: Advanced age (> 50 years); active smoking; high BMI (> 30 kg/m^2); and peripheral artery disease or sensorimotor polyneuropathy. Based on the aforementioned parameters, different selection criteria have been established for the recipients depending on the type of pancreas transplantation. Knowledge of the risk factors for pancreas transplantation allows the establishment of reliable selection criteria for choosing donors and recipients.

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Core Tip: Pancreas transplantation remains the only treatment to restore euglycemia and hemoglobin A1c levels in diabetic patients. However, it presents high morbidity due to different postoperative complications and the effects of the immunosuppressive therapies. The pancreas transplantation complications occur more frequently in specific cases related to donor factors (high body mass index, older age, *etc.*). Several studies analyzed the donor and recipient risk factors. Knowing these risk factors allows us to establish specific selection criteria in pancreas transplantation and may improve its results.

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INTRODUCTION

A simple analysis of the donor's cause of death allowed us to verify that those ideal pancreas donors (healthy and young individuals) are currently decreasing. Therefore, it is very important to optimize all possible pancreas grafts without risking the graft or recipient.

The postoperative complications inherent to pancreatic surgery (*e.g.*, pancreatitis, fistulas, necrosis, *etc.*) appear similarly in pancreas transplantation. In addition, ischemia-reperfusion injury, immunological factors and immunosuppressive therapy increase the risk of their appearance[1]. Therefore, the quality of the graft is essential to reduce the rate of postoperative surgical complications such as thrombosis, pancreatitis, infection and fistulas. The factors discussed below have been associated to an increase in the incidence of technical complications and are still considered a significant cause of pancreatic graft loss[1-3].

DONOR RISK FACTORS

Age of the donors

Donor's age is an important factor in the viability of grafts in all types of transplants. Currently, older donors (> 80 years) are accepted for liver and kidney transplant. Nonetheless, the age in pancreas transplantation remains a strict selection criteria. The use of pediatric donors (< 18 years in the United States) for adult recipients is infrequent due to the fact that these grafts present a lower β-cell mass, require a greater technical challenge and are associated with a greater number of complications, especially vascular thrombosis[4]. Despite this, some authors have presented excellent results using the pancreas from donors < 10 years[5,6].

The largest published series of pancreas donors with ages ranging from 3 to 17 years was from Fernandez LA *et al*[7]. A comparative study was performed between the group of transplants from young donors [142 simultaneous pancreas kidney (SPK) transplantations] and those from adult donors (538 SPK transplantations) over the same period. After ten years of follow-up, no significant differences were found regarding patient survival. However, a trend towards increased graft survival in pediatric pancreas recipients was observed[7]. A subsequent study of the same group insisted on the safety of pancreas transplantation from pediatric donors over three years of age and with a weight of ≥ 25 kg[8]. Some authors have hypothesized that these donors may benefit recipients who are underweight because kidney and pancreatic function could be maximized[9].

Regarding the upper age limit, numerous authors have shown that the using the

pancreas from donors older than 45 years is the most important donor risk factor and leads to reduced graft survival and increased complications[10-19]. Other studies performed under an immunosuppression regimen based on tacrolimus did not find an increase in post-transplant complications using the pancreas from donors ≥ 45 years[11].

Most groups consider using the pancreas of donors older than 45-50 years to present a significant risk in the development of vascular thrombosis, intra-abdominal infections and duodenal or anastomotic leaks, which affects the graft and recipient survival[6,12-22]. Krieger *et al*[6] analyzed 91 SPK transplantations using grafts from donors older than 45 years. There was a decrease in patient survival at 1 year and 5 years and an increase in the percentage of intra-abdominal infections compared to the group transplanted with donor grafts between 18 years and 45 years. Graft loss occurred mostly in the first 2 wk after surgery. This occurred in 6.6% of recipients from older donors compared to 1.9% in the standard group.

These data show the trend to use the pancreas from donors younger than 50 years. This was recently corroborated by the report of the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients published in 2019 in reference to the year 2017[23]. This report stated that the age range of pancreas donors between 18 and 34 years has remained stable for more than a decade. It is the most frequent group of donors with an overall frequency of more than 60% of the transplants. In relation to the other groups, donors under the age of 18 years obtained percentages of around 20%, and those between 35 years and 49 years have decreased in the last 10 years to around 10%. The proportion of donors over 50 years was less than 1% of total pancreas donors[23].

In contrast, the EXPAND multicenter study[24] showed similar rates of morbidity and graft rejection in transplant patients from donors over 50 years compared to those under 50 years. Therefore, in cases of pancreas donors over 45 years, each group should individualize each case by studying the medical history (especially previous cardiovascular diseases), weight, previous physical activity and lifestyle, cause of death, time in the intensive care unit, *etc*. This will allow optimization of a currently scarce resource.

Cause of death for the donor

The ideal donor for pancreas transplantation is a young man without associated diseases who has died by trauma. Currently, the North American and Spanish registries have shown a progressive trend towards older donors with stroke-related causes of death. In addition, the use of grafts from young donors associated with road traffic accident-related deaths is declining.

In one study from the University of Minnesota[25], donor death due to stroke appeared as an independent risk factor for allograft thrombosis after an SPK transplantation. However, the donors were not divided by age groups. Therefore, these results should be taken cautiously because the thrombosis could be related to age and not to the cause of death. In fact, the pancreas of young donors who died of congenital brain damage progressed significantly better than those of donors older than 45 who died by stroke. It seems evident that the existence of coronary artery disease and intracranial atherosclerosis are associated with systemic vascular involvement. Therefore, the cause of death would not be a risk factor in itself but rather the vascular disease.

Hyperglycemia

The presence of hyperglycemia in brain-dead patients is not uncommon. Some authors suggest that hyperglycemia may affect post-transplantation evolution, but in general this status is independent of the endocrine functional state of the pancreas. The hyperglycemic status of the donor has different origins. It may be related to the trauma itself (as a consequence of the destruction of areas of the central nervous system related to metabolic functions), result from acute injury and the secondary release of catecholamines and steroids or it may be related to the administration of exogenous glucose and steroids. In the absence of a history of diabetes, this hyperglycemia is not a contraindication to donation[10,26-28].

Hyperamylasemia

Hight levels of amylase in the blood are observed in up to 40% of donors and may sometimes contraindicate donation[29]. Hyperamylasemia is frequently associated with death due to traumatic brain injury. Other times it occurs as a result of direct trauma to the salivary glands. It may also be secondary to pancreatitis, metastasis and chronic renal disease, contraindicating donation in all cases. Conversely, an isolated elevation

of amylase in the blood without associated lesions is not a contraindication for donation, as the use of this type of pancreas does not affect graft function after transplantation[26-30]. Currently, hyperglycemia or hyperamylasemia are not considered absolute contraindications for transplantation[6,31].

Cold ischemia time

It has been considered that a pancreatic graft can be transplanted up to 30 h after pancreas extraction[32]. Several studies show that within this limit there is no added morbidity[10,15,33,34]. However, other authors have reported an increase in the incidence of complications such as anastomotic leaks, thrombosis, pancreatitis and infections, and they recommended to not exceed the limit of 20 h[35-38]. Recent studies showed a higher rate of graft failure when the cold ischemia time increased[39].

The development of early pancreatitis after transplantation has been associated with several factors, including advanced age and high body mass index (BMI), but it has also been associated with prolonged ischemic times[37,40-42]. Currently, it would be advisable in the brain-dead organ donors a cold ischemia time less than 12 h, and in the donors after circulatory death (category III of the Maastricht classification revisited) a time of cold ischemia less than 8 h.

Cardiac arrest and vasopressors

Donors who are hemodynamically unstable at the time of extraction are considered marginal. In general terms, this corresponds to those donors who require high doses of dopamine (> 10 μg/kg/min) or the use of two vasopressors at the time of extraction. The pancreas is a low-flow organ, so hemodynamic instability before or during extraction may contribute to the presence of inadequate perfusion and the development of graft thrombosis and postoperative pancreatitis[31]. In a donor's preprocurement cardiac arrest, the functional impact and evolutionary curve over time of liver and pancreatic enzymes should be carefully evaluated to rule out severe damage in both organs. In particular, in brain-dead organ donors, the time of preprocurement cardiac arrest should not exceed 15 min, although the functional impact should always be assessed individually.

Macroscopic aspect

The macroscopic appearance of the pancreas at the time of extraction is the most relevant data to decide the graft's viability. The presence of acute or chronic pancreatitis signs, the existence of pseudocysts or an important fatty infiltration may contraindicate the pancreatic extraction. Also, evidence of traumatic injury to the pancreas is contraindicated for transplantation. The pancreatic edema may be the result of overhydration of the donor during the intensive care unit stay. The use of grafts with edema depend on the direct examination by the surgeon and the improvement of the organ after the administration of albumin and diuretics.

The most important factor for deciding the validity of the pancreas remains the inspection by a senior transplant surgeon. A pancreas with calcifications, fibrosis or fatty infiltration should not be considered valid. Likewise, the existence of vessels with intense atheromatosis is an undoubted risk factor[6,31]. During extraction, color, consistency and the presence of masses, nodules or trauma of the pancreas should be evaluated. The organ should have a soft consistency with no indurated areas on palpation and little or no fatty infiltration. A pale coloration suggests ischemia, while an intense yellow color may be a consequence of fatty infiltration related to obesity or alcoholism.

Donor weight

Donor obesity is an important risk factor for surgical complications following transplantation. These grafts present intra- and periglandular fatty infiltration. Therefore, its preservation is not always optimal. These pancreases are more susceptible to ischemia-reperfusion injury and have an increased incidence of pancreatitis, thrombosis and intra-abdominal infections. Likewise, the role that the possible subclinical diabetes of the obese donor may play in the subsequent function of the graft has been highlighted[8].

Previous studies showed significant differences in pancreatic graft survival results between donors with BMI greater than or less than 30 kg/m^2[43]. Other authors found a relationship between a BMI greater than 30 kg/m^2 and the presence of peripancreatic fluid collections[44]. According to most of the authors, donor obesity is considered to be one of the factors that contraindicate the use of the pancreas graft. It therefore seems advisable not to accept a pancreas from a donor with a BMI > 30 kg/m^2[34,35,37].

A lower donor weight also represents a risk factor. The presence of small vessels increases the technical requirements. A recipient with a pancreas from a donor weighing less than 30 kg showed significantly lower graft survival than a recipient who received a graft from a heavier donor. Graft thrombosis was the main cause of graft loss on these occasions[4,8].

RECIPIENT (RISK FACTORS)

Patient selection for SPK transplantation

There are well-defined criteria for selecting SPK transplantation recipients: (1) Age ≤ 55 years. Patients of older age should be considered individually; (2) Absence of severe peripheral arterial disease or coronary heart disease; (3) Absence of several motor sensory neuropathy or peripheral autonomic impairment; (4) Fulfillment of the kidney transplantation criteria; (5) Absence of severe mental disorders; and (6) Ability to understand the possible post-surgery complications and the treatment follow-up[37,45].

Relative contraindications: (1) Patients ≤ 18 years or > 55 years; (2) Recent retinal hemorrhage; (3) Active smoker (it is recommended to stop smoking prior to the inclusion on the waiting list); (4) BMI ≥ 30 kg/m^2; and (5) Human immunodeficiency virus, hepatitis C virus or hepatitis B virus positive. (hepatitis C virus treatment is recommended prior to the inclusion on the waiting list).

Before SPK transplantation, dialysis can be performed by hemodialysis or peritoneal dialysis based on what is considered adequate for the patient depending on the moment and time expected on the waiting list. If the patient's selection criteria are based on achieving the improvement of diabetic lesions, predialysis patients should be recommended for SPK transplantation. Patients with end stage renal disease without dialysis could be included in the waiting list when creatinine levels are lower than 30 mL/min (stage IV). Once included on the waiting list, the nephrologist must report any changes regarding the SPK transplantation selection criteria.

Pancreas transplant indications after a kidney transplant (pancreas after kidney)

Patients suitable for this transplant must meet the following criteria: (1) Type 1 diabetes mellitus (DM): Previous living or deceased donor kidney transplantation; (2) Pancreatic graft failure after an SPK transplantation; (3) Tolerance for an increase in immunosuppressive therapy; and (4) Stable performance of the renal graft in all the cases (creatinine clearance > 40 mL/min)[37,46].

Pancreas transplant alone

Pancreas transplant alone is recommended for type 1 DM patients without end stage renal disease. Also, a creatinine clearance > 60 mL/min and a proteinuria < 2 g/d are required. Inclusion criteria: (1) Uncontrolled DM (severe hypoglycemia, hyperglycemia or ketoacidosis) that compromise the quality of life; and (2) Failure of the continuous subcutaneous insulin infusion and continuous glucose monitoring[37,47].

Indications in type 2 DM and other types of diabetes (maturity-onset diabetes of the young)

Pancreas transplantation within these patients is limited to a stringent group. Survival of the patients and grafts are similar to type 1 DM if the following selection criteria are fulfilled: (1) 5 or more years with insulin therapy; (2) Insulin requirements < 75 IU/d; (3) BMI ≤ 30 kg/m^2; and (4) Fulfillment of type 1 DM indications[37].

Patients with a lower insulin secretion should be noted. Although it is hard to establish these values based on the C-peptide values, a feasible option could be considering C-peptide values < 5 ng/mL.

Patient assessment for pancreas transplantation

The following assessments are completed prior to pancreas transplantation: (1) Medical history, physical examination, previous red blood cell transfusions, *etc.*; (2) Immunological studies: Blood type, human leukocyte antigen, cytotoxic antibodies, luminex, *etc.*; (3) Radiological exams: Abdominal ultrasound and chest and abdominal X-ray; (4) Endoscopic procedures: Colonoscopy in patients ≥ 50 years old included on the waiting list; (5) Extensive blood test including evaluation of diabetes, viral serology and prostate specific antigen in male patients older than 40 years; and (6) In patients with a history of autoimmune diseases (lupus, vasculitis, *etc.*), deep vein thrombosis, pulmonary embolism, acute stroke, heart attack or family history of venous

thromboembolism, a complete study of thrombophilia should be performed[37,48,49].

For each patient, besides the aforementioned clinical data and physical examination, a specific complication-oriented study should be performed: (1) Diabetic retinopathy screening (data regarding photocoagulation treatment and possible surgical interventions should be stored); (2) Cardiovascular evaluation: we followed the upcoming algorithm to identify the status of coronary heart disease in all pancreas transplant candidates[49] (Figure 1); (3) Assessment of the peripheral vascular disease. Evaluation of iliac axis by a computed tomographic angiography or magnetic resonance angiography. Moreover, a carotid and aortic-iliac duplex ultrasound should be performed in all patients; (4) Urological status: each recipient should be assessed by the Urology Service to assess the urological status due to the diabetic autonomic neuropathy. A prostate exam should be performed in males > 40 years; (5) Neurological evaluation: clinical assessment of the peripheral neuropathy, the nerve conduction velocity and the autonomic status; (6) Hormonal studies, C-peptide measurement and immunological markers of the DM (anti-insulin and anti-GAD antibodies); (7) Gynecological examination in fertile females (a mammography and vaginal cytology should be included in females > 35 years); (8) Evaluation by the pancreas transplant surgery team: assessment of the intestinal function, existence of associated diseases such as gallstones, state of vascular axis and previous abdominal surgery; (9) Complete infectious diseases screening; and (10) Psychological evaluation (if needed).

Contraindications of pancreas transplantation (SPK, pancreas after kidney, pancreas transplant alone transplantations)

The following items are contraindications of a pancreas transplantation: (1) Active infection; (2) Severe coagulation abnormalities; (3) Positive crossmatch; (4) Drug addiction (including alcoholism); (5) Complex coronary artery lesions, ejection fraction < 50% and recent myocardial infarction; (6) Previous history of treatment noncompliance; (7) Severe psychiatric disorder; (8) Neoplasia; (9) Morbid obesity; and (10) Previously indicated contraindications in the kidney-pancreas transplant selection criteria[37].

CONCLUSION

Knowledge of the risk factors for pancreas transplantation allows the establishment of reliable selection criteria for choosing donors and recipients.

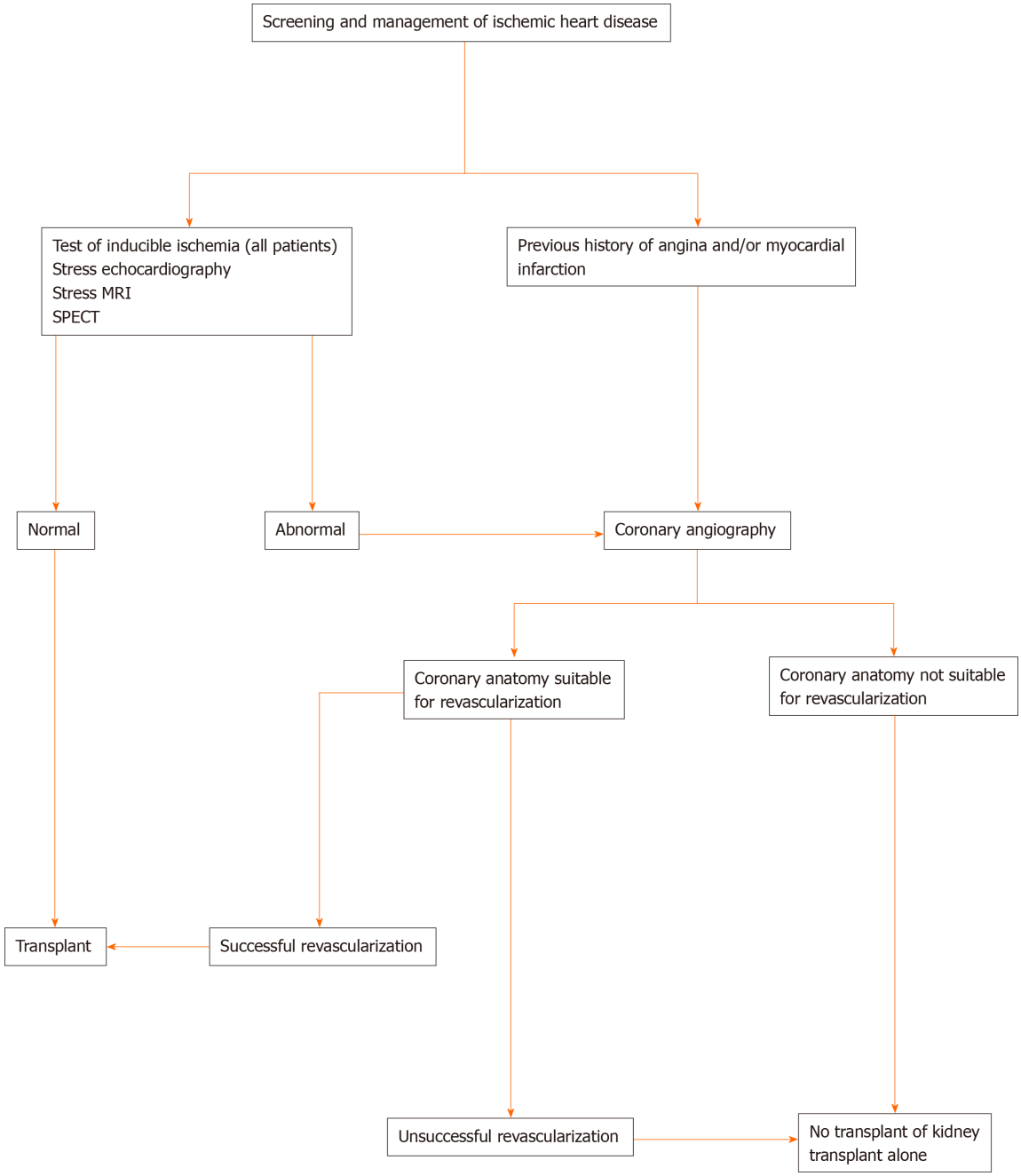

Figure 1 Algorithm to identify the status of coronary heart disease in all pancreas transplant candidates. MRI: Magnetic resonance imaging; SPECT: Single-photon emission computed tomography.

REFERENCES

1 **Sutherland DE**, Gruessner RW, Dunn DL, Matas AJ, Humar A, Kandaswamy R, Mauer SM, Kennedy WR, Goetz FC, Robertson RP, Gruessner AC, Najarian JS. Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann Surg* 2001; **233**: 463-501 [PMID: 11303130 DOI: 10.1097/00000658-200104000-00003]

2 **Sutherland DE**, Gruessner R, Gillingham K, Moudry-Munns K, Dunn D, Brayman K, Morel P, Najarian JS. A single institution's experience with solitary pancreas transplantation: a multivariate analysis of factors leading to improved outcome. *Clin Transpl* 1991: 141-152 [PMID: 1820112]

3 **Cicalese L**, Giacomoni A, Rastellini C, Benedetti E. Pancreatic transplantation: a review. *Int Surg* 1999; **84**: 305-312 [PMID: 10667809]

4 **Schulz T**, Schenker P, Flecken M, Kapischke M. Donors with a maximum body weight of 50 kg for simultaneous pancreas-kidney transplantation. *Transplant Proc* 2005; **37**: 1268-1270 [PMID: 15848691 DOI: 10.1016/j.transproceed.2004.12.252]

5 **Van der Werf WJ**, Odorico J, D'Alessandro AM, Knechtle S, Becker Y, Collins B, Pirsch J, Hoffman R, Sollinger HW. Utilization of pediatric donors for pancreas transplantation. *Transplant Proc* 1999; **31**: 610-611 [PMID: 10083258 DOI: 10.1016/s0041-1345(98)01578-4]

6 **Krieger NR**, Odorico JS, Heisey DM, D'Alessandro AM, Knechtle SJ, Pirsch JD, Sollinger HW. Underutilization of pancreas donors. *Transplantation* 2003; **75**: 1271-1276 [PMID: 12717215 DOI: 10.1097/01.TP.0000061603.95572.BF]

7 **Fernandez LA**, Turgeon NA, Odorico JS, Leverson G, Pirsch JD, Becker BN, Chin LT, Becker YT, Knechtle SJ, Foley DP, Shames BD, Kalayoglu M, D'Alessandro AM, Sollinger HW. Superior long-term results of simultaneous pancreas-kidney transplantation from pediatric donors. *Am J Transplant* 2004; **4**: 2093-2101 [PMID: 15575914 DOI: 10.1046/j.1600-6143.2004.00599.x]

8 **Neidlinger NA**, Odorico JS, Sollinger HW, Fernandez LA. Can 'extreme' pancreas donors expand the donor pool? *Curr Opin Organ Transplant* 2008; **13**: 67-71 [PMID: 18660709 DOI: 10.1097/MOT.0b013e3282f44a51]

9 **Rhein T**, Metzner R, Uhlmann D, Serr F, Caca K, Weinert D, Hauss J, Witzigmann H. Pediatric donor organs for pancreas transplantation: an underutilized resource? *Transplant Proc* 2003; **35**: 2145-2146 [PMID: 14529870 DOI: 10.1016/s0041-1345(03)00749-8]

10 **Gruessner AC**, Barrou B, Jones J, Dunn DL, Moudry-Munns K, Najarian JS, Sutherland DE, Gruessner RW. Donor impact on outcome of bladder-drained pancreas transplants. *Transplant Proc* 1993; **25**: 3114-3115 [PMID: 8266477]

11 **Bonham CA**, Kapur S, Dodson SF, Dvorchik I, Corry RJ. Potential use of marginal donors for pancreas transplantation. *Transplant Proc* 1999; **31**: 612-613 [PMID: 10083259 DOI: 10.1016/s0041-1345(98)01579-6]

12 **Odorico JS**, Heisey DM, Voss BJ, Steiner DS, Knechtle SJ, D'Alessandro AM, Hoffmann RM, Sollinger HW. Donor factors affecting outcome after pancreas transplantation. *Transplant Proc* 1998; **30**: 276-277 [PMID: 9532034 DOI: 10.1016/s0041-1345(97)01263-3]

13 **Douzdjian V**, Gugliuzza KG, Fish JC. Multivariate analysis of donor risk factors for pancreas allograft failure after simultaneous pancreas-kidney transplantation. *Surgery* 1995; **118**: 73-81 [PMID: 7604382 DOI: 10.1016/s0039-6060(05)80012-1]

14 **Douzdjian V**, Rice JC, Carson RW, Gugliuzza KG, Fish JC. Renal allograft failure after simultaneous pancreas-kidney transplantation: univariate and multivariate analyses of donor and recipient risk factors. *Clin Transplant* 1996; **10**: 271-277 [PMID: 8826665]

15 **Troppmann C**, Gruessner AC, Benedetti E, Papalois BE, Dunn DL, Najarian JS, Sutherland DE, Gruessner RW. Vascular graft thrombosis after pancreatic transplantation: univariate and multivariate operative and nonoperative risk factor analysis. *J Am Coll Surg* 1996; **182**: 285-316 [PMID: 8605554]

16 **Troppmann C**, Gruessner AC, Papalois BE, Sutherland DE, Matas AJ, Benedetti E, Gruessner RW. Delayed endocrine pancreas graft function after simultaneous pancreas-kidney transplantation. Incidence, risk factors, and impact on long-term outcome. *Transplantation* 1996; **61**: 1323-1330 [PMID: 8629291 DOI: 10.1097/00007890-199605150-00007]

17 **Troppmann C**, Gruessner AC, Dunn DL, Sutherland DE, Gruessner RW. Surgical complications requiring early relaparotomy after pancreas transplantation: a multivariate risk factor and economic impact analysis of the cyclosporine era. *Ann Surg* 1998; **227**: 255-268 [PMID: 9488525 DOI: 10.1097/00000658-199802000-00016]

18 **Humar A**, Kandaswamy R, Granger D, Gruessner RW, Gruessner AC, Sutherland DE. Decreased surgical risks of pancreas transplantation in the modern era. *Ann Surg* 2000; **231**: 269-275 [PMID: 10674620 DOI: 10.1097/00000658-200002000-00017]

19 **Gruessner AC**, Sutherland DE. Analysis of United States (US) and non-US pancreas transplants reported to the United network for organ sharing (UNOS) and the international pancreas transplant registry (IPTR) as of October 2001. *Clin Transpl* 2001: 41-72 [PMID: 12211799]

20 **Boggi U**, Del Chiaro M, Signori S, Vistoli F, Amorese G, Croce C, Morelli L, Vanadia Bartolo T, Pietrabissa A, Barsotti M, Rizzo G, Mosca F. Pancreas transplants from donors aged 45 years or older. *Transplant Proc* 2005; **37**: 1265-1267 [PMID: 15848690 DOI: 10.1016/j.transproceed.2005.01.027]

21 **Boggi U**, Del Chiaro M, Vistoli F, Signori S, Vanadia Bartolo T, Gremmo F, Marchetti P, Coppelli A, Rizzo G, Mosca F. Pancreas transplantation from marginal donors. *Transplant Proc* 2004; **36**: 566-568 [PMID: 15110595 DOI: 10.1016/j.transproceed.2004.02.031]

22 **Salvalaggio PR**, Schnitzler MA, Abbott KC, Brennan DC, Irish W, Takemoto SK, Axelrod D, Santos LS, Kocak B, Willoughby L, Lentine KL. Patient and graft survival implications of simultaneous pancreas kidney transplantation from old donors. *Am J Transplant* 2007; **7**: 1561-1571 [PMID: 17511681 DOI: 10.1111/j.1600-6143.2007.01818.x]

23 **Kandaswamy R**, Stock PG, Gustafson SK, Skeans MA, Curry MA, Prentice MA, Fox A, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2016 Annual Data Report: Pancreas. *Am J Transplant* 2018; **18** Suppl 1: 114-171 [PMID: 29292605 DOI: 10.1111/ajt.14558]

24 **Kandaswamy R**, Stock PG, Gustafson SK, Skeans MA, Urban R, Fox A, Odorico JS, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2017 Annual Data Report: Pancreas. *Am J Transplant* 2019; **19** Suppl 2: 124-183 [PMID: 30811891 DOI: 10.1111/ajt.15275]

25 **Gruessner RW**, Sutherland DE, Troppmann C, Benedetti E, Hakim N, Dunn DL, Gruessner AC. The surgical risk of pancreas transplantation in the cyclosporine era: an overview. *J Am Coll Surg* 1997; **185**: 128-144 [PMID: 9249080 DOI: 10.1016/s1072-7515(01)00895-x]

26 **Vinkers MT**, Rahmel AO, Slot MC, Smits JM, Schareck WD. How to recognize a suitable pancreas donor: a Eurotransplant study of preprocurement factors. *Transplant Proc* 2008; **40**: 1275-1278 [PMID: 18589086 DOI: 10.1016/j.transproceed.2008.03.142]

27 **Axelrod DA**, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas

allograft quality, outcomes and geographic variation in utilization. *Am J Transplant* 2010; **10**: 837-845 [PMID: 20121753 DOI: 10.1111/j.1600-6143.2009.02996.x]

28 **Schenker P**, Vonend O, Ertas N, Wunsch A, Viebahn R. Preprocurement pancreas allocation suitability score does not correlate with long-term pancreas graft survival. *Transplant Proc* 2010; **42**: 178-180 [PMID: 20172309 DOI: 10.1016/j.transproceed.2009.12.036]

29 **Hesse UJ**, Sutherland DE. Influence of serum amylase and plasma glucose levels in pancreas cadaver donors on graft function in recipients. *Diabetes* 1989; **38** Suppl 1: 1-3 [PMID: 2463194 DOI: 10.2337/diab.38.1.s1]

30 **Nghiem DD**, Cottington EM, Corry RJ. Pancreas donor criteria. *Transplant Proc* 1988; **20**: 1007-1009 [PMID: 3055473]

31 **Kapur S**, Bonham CA, Dodson SF, Dvorchik I, Corry RJ. Strategies to expand the donor pool for pancreas transplantation. *Transplantation* 1999; **67**: 284-290 [PMID: 10075595 DOI: 10.1097/00007890-199901270-00017]

32 **Wright FH**, Wright C, Ames SA, Smith JL, Corry RJ. Pancreatic allograft thrombosis: donor and retrieval factors and early postperfusion graft function. *Transplant Proc* 1990; **22**: 439-441 [PMID: 1691538]

33 **Schmid T**, Königsrainer A, Steiner E, Koller J, Margreiter R. Do donor age and cold-ischemia time have a detrimental effect on early pancreas-allograft function? *Diabetes* 1989; **38** Suppl 1: 4-6 [PMID: 2642855 DOI: 10.2337/diab.38.1.s4]

34 **D'Alessandro AM**, Stratta RJ, Sollinger HW, Kalayoglu M, Pirsch JD, Belzer FO. Use of UW solution in pancreas transplantation. *Diabetes* 1989; **38** Suppl 1: 7-9 [PMID: 2463200 DOI: 10.2337/diab.38.1.s7]

35 **Humar A**. Pancreas donors. *Curr Opin Organ Transplant* 2007; **12**: 73-76 [PMID: 27792093 DOI: 10.1097/MOT.0b013e328012dd88]

36 **Humar A**, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AC, Sutherland DE. Technical failures after pancreas transplants: why grafts fail and the risk factors--a multivariate analysis. *Transplantation* 2004; **78**: 1188-1192 [PMID: 15502718 DOI: 10.1097/01.tp.0000137198.09182.a2]

37 **National Transplant Organization**. Documento de consenso sobre criterios de selección de donante y receptor en trasplante de páncreas. [Internet]. 2018. Available from: http://www.ont.es/infesp/DocumentosDeConsenso/Doc.Consenso Criterios Selección Don y Recep Tx Páncreas3.pdf

38 **Montero N**, Webster AC, Royuela A, Zamora J, Crespo Barrio M, Pascual J. Steroid avoidance or withdrawal for pancreas and pancreas with kidney transplant recipients. *Cochrane Database Syst Rev* 2014; (9): CD007669 [PMID: 25220222 DOI: 10.1002/14651858.CD007669.pub2]

39 **Rudolph EN**, Dunn TB, Sutherland DER, Kandaswamy R, Finger EB. Optimizing outcomes in pancreas transplantation: Impact of organ preservation time. *Clin Transplant* 2017; **31** [PMID: 28636074 DOI: 10.1111/ctr.13035]

40 **Benedetti E**, Gruessner AC, Troppmann C, Papalois BE, Sutherland DE, Dunn DL, Gruessner RW. Intra-abdominal fungal infections after pancreatic transplantation: incidence, treatment, and outcome. *J Am Coll Surg* 1996; **183**: 307-316 [PMID: 8843258]

41 **Khubutia MS**, Pinchuk AV, Dmitriev IV, Balkarov AG, Storozhev RV, Anisimov YA. Surgical complications after simultaneous pancreas-kidney transplantation: A single-center experience. *Asian J Surg* 2016; **39**: 232-237 [PMID: 26857852 DOI: 10.1016/j.asjsur.2015.11.003]

42 **Lakey JR**, Warnock GL, Rajotte RV, Suarez-Alamazor ME, Ao Z, Shapiro AM, Kneteman NM. Variables in organ donors that affect the recovery of human islets of Langerhans. *Transplantation* 1996; **61**: 1047-1053 [PMID: 8623183 DOI: 10.1097/00007890-199604150-00010]

43 **Humar A**, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AG, Sutherland DE. The impact of donor obesity on outcomes after cadaver pancreas transplants. *Am J Transplant* 2004; **4**: 605-610 [PMID: 15023153 DOI: 10.1111/j.1600-6143.2004.00381.x]

44 **Singh RP**, Vrakas G, Hayek S, Hayek S, Anam S, Aqueel M, Olsburgh J, Calder F, Mamode N, Callaghan C, Kessaris N, Pattison J, Hilton R, Koffman G, Taylor JD, Drage MW. Clinically significant peripancreatic fluid collections after simultaneous pancreas-kidney transplantation. *Transplantation* 2013; **95**: 1263-1269 [PMID: 23507700 DOI: 10.1097/TP.0b013e318289c978]

45 **Redfield RR**, Scalea JR, Odorico JS. Simultaneous pancreas and kidney transplantation: current trends and future directions. *Curr Opin Organ Transplant* 2015; **20**: 94-102 [PMID: 25565444 DOI: 10.1097/MOT.0000000000000146]

46 **Siskind E**, Maloney C, Akerman M, Alex A, Ashburn S, Barlow M, Siskind T, Bhaskaran M, Ali N, Basu A, Molmenti E, Ortiz J. An analysis of pancreas transplantation outcomes based on age groupings--an update of the UNOS database. *Clin Transplant* 2014; **28**: 990-994 [PMID: 24954160 DOI: 10.1111/ctr.12407]

47 **Redfield RR**, Rickels MR, Naji A, Odorico JS. Pancreas Transplantation in the Modern Era. *Gastroenterol Clin North Am* 2016; **45**: 145-166 [PMID: 26895686 DOI: 10.1016/j.gtc.2015.10.008]

48 **Alhamad T**, Stratta RJ. Pancreas-kidney transplantation in diabetes mellitus: Patient selection and pretransplant evaluation. [Internet]. Available from: https://www.uptodate.com/contents/pancreas-kidney-transplantation-in-diabetes-mellitus-patient-selection-and-pretransplant-evaluation

49 **Mangus RS**, Powelson J, Kinsella SB, Farar DT, Creal CA, Fridell JA. Pretransplant coronary artery disease associated with worse clinical outcomes in pancreas transplantation. *Clin Transplant* 2013; **27**: E442-E447 [PMID: 23923972 DOI: 10.1111/ctr.12185]

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MINIREVIEWS

Complications during multiorgan retrieval and pancreas preservation

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Abstract

In pancreas transplantation, complications can arise at each step of the process, from the initial selection of donors and recipients through the surgical technique itself and the post-operative period, when lifelong immunosuppression is required. In the early steps, careful retrieval and preservation of the pancreas are crucial for the viability of the organ and ultimate success of the transplant. The pancreas is a low-flow gland, making it highly sensitive to transplantation conditions and presenting risk of pancreatitis due to periods of ischemia. The two groups of donors - after brain death (DBD) or after cardiac arrest (DCD) - require different strategies of retrieval and preservation to avoid or reduce the risk of complications developing during and after the transplantation. For DBD donor transplantation, multiorgan retrieval and cold preservation is the conventional technique. Asystole donor (DCD) transplantation, in contrast, can benefit from the newest technologies, such as hypothermic and especially normothermic preservation machines (referred to as NECMO), to optimize organ preservation. The latter has led to an increase in the pool of donors by facilitating recuperation of organs for transplantation that would have been discarded otherwise.

Key Words: Pancreas transplantation; Diabetes mellitus; Graft thrombosis; Compartmental syndrome; Pancreas retrieval; Pancreas preservation

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Core Tip: The retrieval and preservation steps of pancreas transplantation are critical factors for graft and patient survival. The most frequent complications of these steps are pancreatitis, graft thrombosis, fistula, and infectious collections. Therefore, it is very important to design and carry out a careful surgical technique for retrieval and a rigorous method of preservation for optimal organ integrity.

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INTRODUCTION

The selection requirements for accepting a pancreatic graft are very strict, with the transplant and patient outcomes depending largely on such[1-3]. The most important risk criteria for recipients are age over 55 years, body mass index over 30%, creatinine level over 1.5, preservation period over 20 h, prolonged periods of cardiac arrest and hypotension, and donor factors of atherosclerosis as cause of brain death, presence of arteriosclerosis of the celiac axis, presence of thrombophilia, and history of cardiac arrest[4,5]. The complications that occur during the earliest steps (retrieval and preservation) are determinant factors of the transplant outcome. Early recognition of complications and initiation of preventive measures, therefore, guide the decision-making process for moving forward with any transplantation.

The potential complications are numerous but the most common are postoperative bleeding, graft thrombosis, peripancreatic collections and abscesses, duodenal fistulas, pancreatitis, pseudocyst formation, compartment syndrome, and long-term formation of fungal aneurysms[6-8]. These recipient complications present equal risk with regard to donor status at time of harvesting: Brain dead donor (DBD) or asystole (DCD). These two forms of donor status are determined by the circumstances of the donation situation. DBD, which uses cold-temperature preservation, occurs under the following three scenarios: A1, with unidentified vascular anomalies during the retrieval; A2, with iatrogenic lesions during the retrieval; and A3, with anomalous factors related to the perfusion and preservation. DCD, on the other hand, is classified as either B1, with super-fast retrieval and cold preservation, or B2, with preservation with normothermic preservation machines (NECMOs).

A-DBD (A1-A3) WITH RETRIEVAL AND COLD PRESERVATION

In these scenarios, the pancreatic retrieval technique can be performed by classic dissection, obtaining the pancreas in combination with the liver, or by a technique of removal of the entire abdominal block (liver, pancreas, and kidneys). In most pancreas transplant programs, the type of graft used is the pancreatic-duodenal form obtained from DBDs; although, in some centers, DCDs are used. Moreover, at the end of the century (1980s and 1990s), some centers used segmental grafts, including those obtained from living donors.

Since pancreas donors are often also liver donors, it is mandatory to share both arterial and venous vascularization[9-11]. As such, there are a number of specific factors that determine the viability of a pancreatic graft, such as vascular abnormalities, especially of the hepatic artery, edema or fat infiltration of the pancreas, injuries during harvesting, injuries to the surface of the pancreas, hematomas, *etc*[12-14].

A1 (unidentified vascular anomalies during the retrieval)

The fundamental axis of the arterial circulation is the celiac axis, and the system consists of three main arteries: The splenic artery, the gastroduodenal artery, and the superior mesenteric artery. One of the most frequent vascular anomalies encountered is a right hepatic artery from the upper mesenteric artery (Figures 1 and 2). This anomaly must be detected at the beginning of the retrieval operation, since injury or inadvertent section of this artery compromises the use of one of the associated

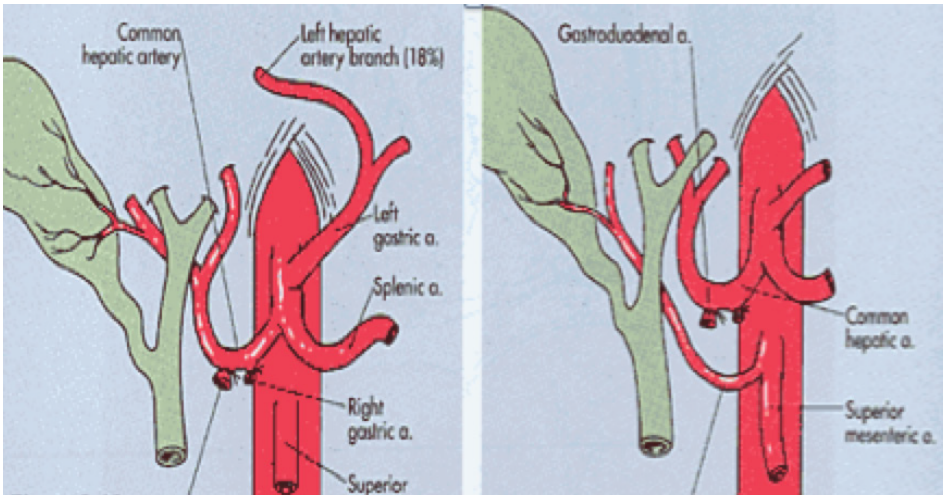

Figure 1 Right hepatic artery from mesenteric superior artery.

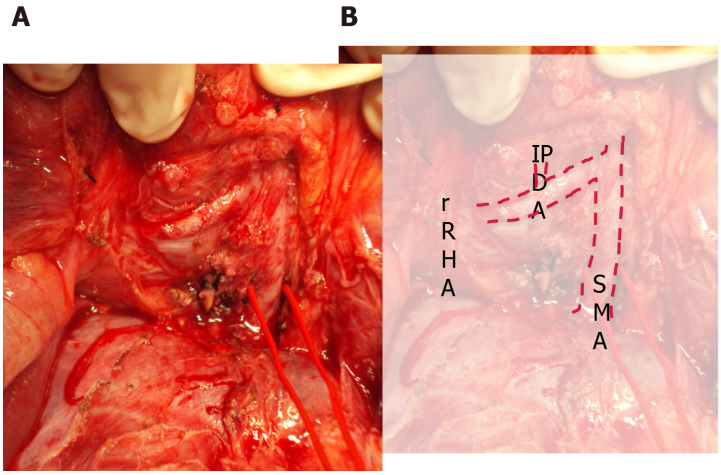

Figure 2 Right hepatic artery from mesenteric superior artery. A: Intraoperative view; B: Overlayed with identifiers. SMA: Superior mesenteric artery; IPDA: Inferior pancreaticoduodenal artery; rRHA: Replaced right hepatic artery.

organs[15,16]. Another frequently encountered anomaly is a dorsal pancreatic artery exiting directly into the celiac trunk or just before the splenic artery (Figure 3); injury of this artery during surgical maneuvers results in graft thrombosis[17].

A2 (iatrogenic lesions during retrieval)

This situation can only be avoided (or risk minimized) by careful performance of the pancreas retrieval technique[18]. In most cases, the situation can be readily recognized by the surgeon during the harvesting procedure and repaired immediately; if it goes undetected until the inspection of the graft during the bench surgery, or even until the time of implantation and revascularization, the consequences can be dire (hematoma and postoperative pancreatitis)[19,20]. From a technical point of view, it is recommended to mobilize the pancreas without touching the gland (as much as possible), holding it through the spleen in order to avoid traction, hematomas and capsule tears (Figure 4).

The most critical injuries are those that involve the vessels of the gland at the pancreas head and duodenum; although, those involving the pancreatic body and tail are not trifling. One of the complications that can occur is related to the anatomical vascular anomalies already mentioned, such as the existence of a right hepatic artery as the first branch of the superior mesenteric artery or the section or injury of a segment of the splenic artery or the dorsal pancreatic artery. If this has occurred and tail perfusion is compromised, at most centers the graft is usually discarded for vascularized transplantation, leaving open the option of use for islet isolation. However, in some emergent situations, such as a rescue surgery, a distal resection could be performed in order to use the graft for vascularized transplant.

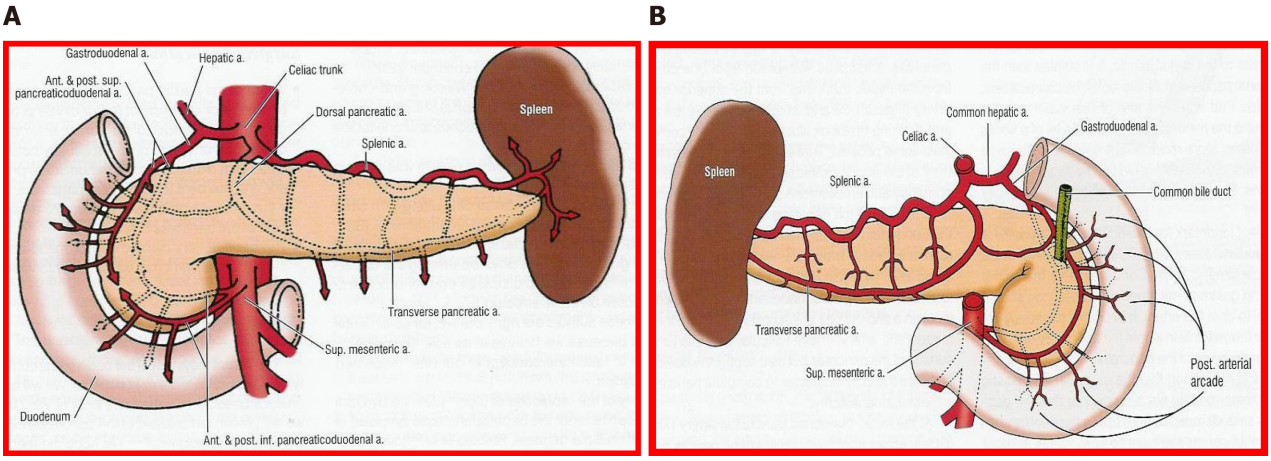

Figure 3 Arterial vasculature of the pancreas. Illustrated from the view of contemporary surgery. A: Anterior; B: Posterior.

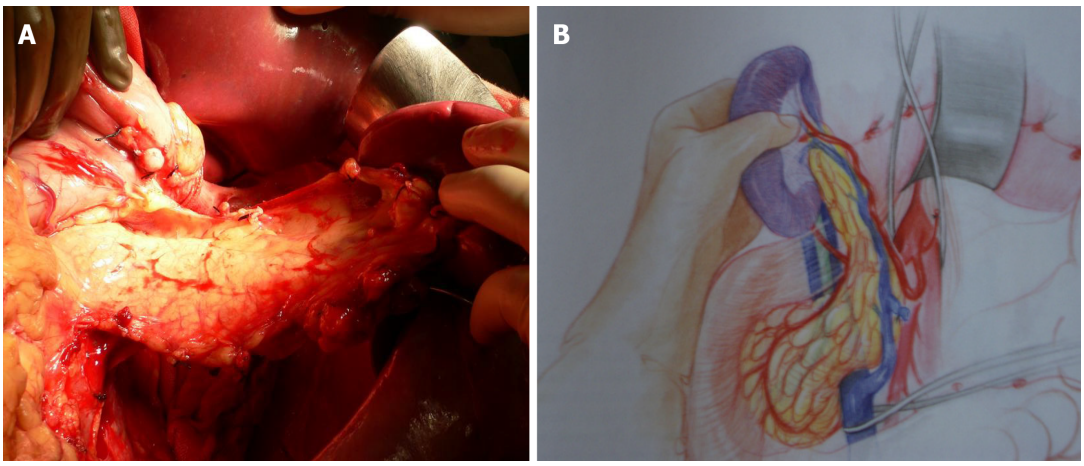

Figure 4 Pancreas graft mobilization. A: Photo; B: Drawing from Martin Finch.

It is convenient to place some sutures that identify the edge of the splenic artery, since it can retract, and also to identify the section edge of the portal vein, given its small size. It is important to check that the lower pancreaticoduodenal artery is located on the pancreatic side entirely; this is especially important during preparation of the duodenal segment of the graft, and during distal section of the mesenteric vessels.

A3 (factors related to the perfusion and preservation of the pancreas)

Static cold storage is the preservation technique used in most programs of pancreas transplants. It is based on the principle of reducing cell metabolism by lowering the temperature. This decreases the consumption of adenosine triphosphate and inhibits the activity of intracellular enzymes, with consequent reduction in cell degradation by hydrolysis of phospholipids. Under the hypothermic condition, metabolism activity drops to 10% but, over time, it produces ischemic lesions. This is particularly detrimental to graft survival, and preservative solutions are designed to minimize the detrimental effects of cold ischemic injury[21,22]. This remains an essential aspect for the surgeon's attention, however, since the pancreas is a gland that is very sensitive to edema.

The perfusion technique must be carried out with any preservation solution [*e.g.*, electrolyte mimicking intracellular, *i.e.*, UW, or extracellular, *i.e.*, IGL, solutions, and mannitol-containing solutions, *i.e.*, Celsior and histidine-tryptophan-ketoglutarate (commonly referred to as HTK), *etc.*] through arterial cannulas at low pressure (< 60 cm) in order to minimize edema[23-27]. In general, it is recommended to perform perfusion through the aorta[9], sectioning the portal vein above the pancreas after having perfused the 1st L of solution, in order to facilitate drainage of the pancreas and avoid edema.

In order to maintain arterial and venous perfusion for the liver, the portal vein

proximal to the liver may be cannulated and perfusion continued. Arterial perfusion should also be continued to maintain the perfusion of the liver and kidneys. A maximum of 4 L of perfusion solution is recommended for a 70 kg donor. Once the pancreas has cooled through the perfusion and *via* contact with ice, it can be retrieved separately or together with the liver (Figures 5 and 6). There is good evidence that both liver and pancreas function better when retrieved en bloc and separated on the back table[10].

In bench surgery, the integrity of the gland and its vessels must be checked. In addition to confirming that the capsule is intact, it is important to infuse preservation solution at low pressure through the cut ends of the splenic and superior mesenteric arteries, to verify that the effluent flows properly through the end of the graft's portal vein. It can also be left without ligating the stump of the gastroduodenal artery to check the permeability of the arterial tree at that level. The venous drainage of the pancreas is made up of vessels that connect to the splenic vein and the superior mesenteric vein, giving way to the portal vein (Figures 7 and 8).

If the perfusion is not satisfactory or the portal effluent remains bloody with small clots, the perfusion is deemed inadequate and a risk for venous thrombosis of the graft[28].

B-DONOR IN ASYSTOLE (DCD) (B1 AND B2)

Shortage of conventional pancreas donors has led to a significant increase in DCD donations. Indeed, asystole donors have constituted a very important group in recent years. The largest studies comparing the outcomes of pancreas transplantation from DCDs with those from DBDs have shown comparable results. However, it is important to remember that the selection of DCDs is often more rigorous and DCDs tend to be younger, with a lower body mass index; and, recipients of such are also at lower-risk immunological level, further favoring the results from DCD transplants[29-32]. Given that the use of these donors implies an increase in resources, we must be extreme in the selection criteria, in order to identify the risk factors and therefore the complications that these donors may present (Table 1). Although there are some differences in the screening and control criteria of these donors in different occidental countries, in general, the 5-min non-touch period is accepted. The technique chosen for organ retrieval depends on whether NECMO technology is available; alternatively, a super-fast cold technique must be used.

B1 (super-fast retrieval and cold preservation)

Super-fast retrieval and cold dissection technique was introduced as a means of rapid procurement of all abdominal organs. This approach was initially used with unstable donors but has since been applied successfully to multiorgan retrievals. In such cases, extreme care must be taken when performing the surgery to avoid iatrogenic injuries. It is very important to check for anatomical anomalies and carry out the surgical technique in conjunction with an early abdominal perfusion through the aorta. After the non-touch period, wide-access laparotomy and rapid access to the aorta should be performed to insert the perfusion cannula[33-35] (Figure 9).

Warm ischemic time has two components - the time from when the patient is hypotensive after the start of life-support limitation, and the time from asystole to cannulation of the abdominal aorta and the start of organ-preserving perfusion. Once the entire abdominal block has been perfused, it should be explanted *en bloc*. Subsequently, the dissection and identification of the different anatomical structures can be performed in the bench surgery. It is convenient to reperfuse the pancreas through the splenic and upper mesenteric arteries, until the effluent becomes clear.

The asystole donor is considered to be at higher thrombotic risk. Pre-transplant anticoagulation with low molecular weight heparin (40 mg at 6 h before surgery) should be performed, followed by heparinization with 2500 U of unfractionated heparin before vascular clamping in the recipient.

B2-donor in asystole (DCD) (with NECMO preservation)

NECMO technology is relatively new but has emerged as a successful approach for the retrieval and preservation of organs from controlled asystole Maastricht type III donors[36-40]. Normothermal perfusion has the potential to decrease or ameliorate ischemic injury and also facilitates the testing of graft viability, reducing the percentage of organs discarded prior to transplantation. Its use in DCDs has been proposed as superior to super-fast extraction, as it overcomes the risk of ischemia

Table 1 Risk factors

No. of risk factors	Tecnical failure (%)	Graft survival (%)
0	7.5	100
1	12.8	92.5
2	26.7	75.9
3	42.9	57.1

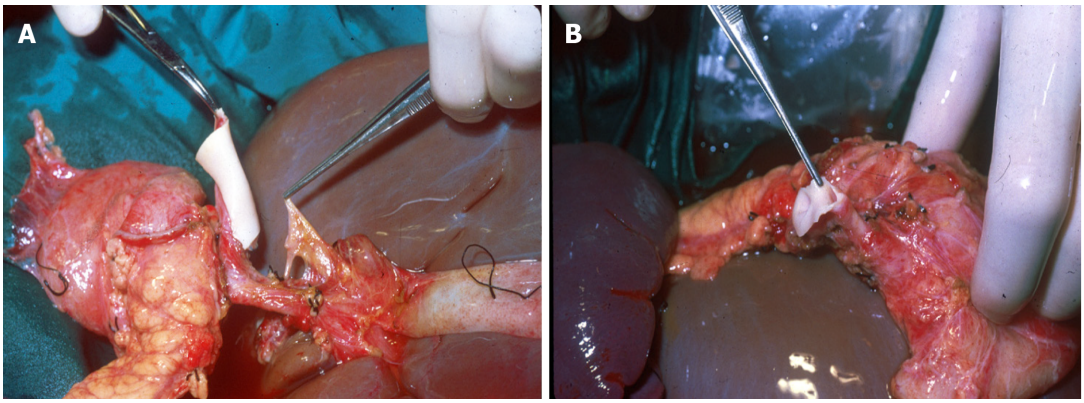

Figure 5 Retrieval of pancreas and liver. A and B: Intraoperative views of the retrieval procedure, showing different aspects.

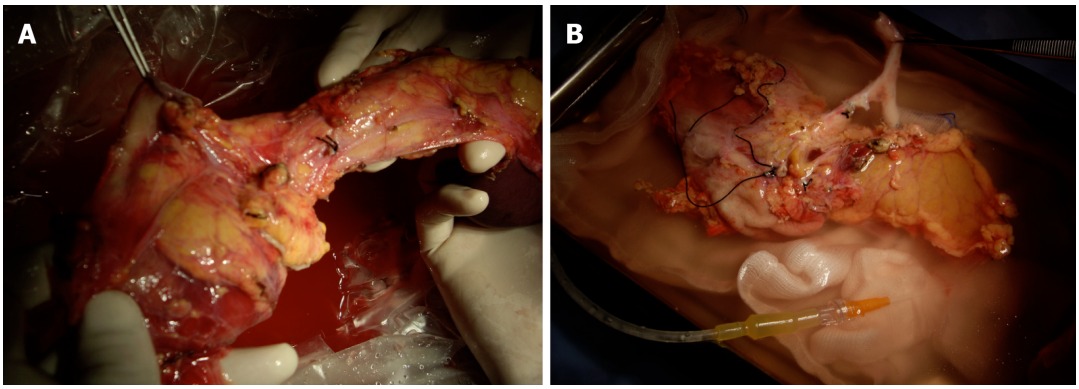

Figure 6 Pancreatico-duodenal graft. A and B: Intraoperative views of the bench preparation procedure, showing different aspects.

effects and improves the graft outcome in recipients. The demonstrated advantages are better immediate graft function, fewer post-transplant complications, shorter hospital stay, and better graft survival. These differences are especially significant in the case of liver and pancreas transplants[41].

One of the important advantages in Spain, in particular, is that it is legally authorized to start anticoagulation maneuvers and placement of cannulas after consent for donation. This process consists of the administration of heparin (600 U/kg) and the cannulation of the femoral vessels before the withdrawal of life-sustaining therapies. The femoral artery and vein are percutaneously cannulated in the intensive care unit, using the Seldinger technique. An aortic occlusion balloon is placed through the femoral vessels in the contralateral groin to prevent cerebral and coronary perfusion during the normothermal recirculation. It is also essential to maintain a pump flow of 2-2.4 L/min[42,43] (Figure 10).

The functional warm ischemic time (commonly known as f-WIT) for abdominal grafts is defined as the time from systolic blood pressure < 60 mmHg to the start of normothermal recirculation, including the 5-min non-touch period. A continuous pressure of 60-65 mmHg should be maintained at the femoral artery cannula, along with a temperature of 37 °C. Bicarbonate is administered immediately after the start of recirculation, to maintain pH of 7.35-7.45. Hematocrit is maintained > 25%. To avoid

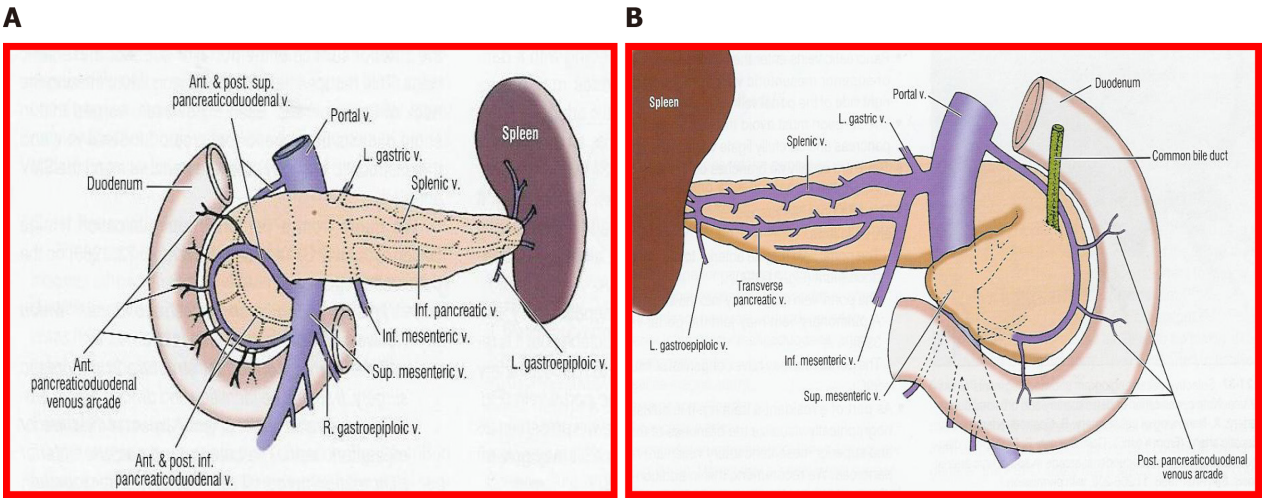

Figure 7 Venous vessels. Illustrated from the view of contemporary surgery. A: Anterior view; B: Posterior view.

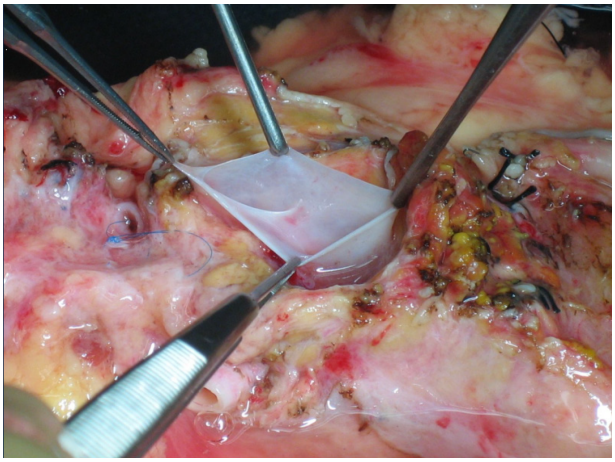

Figure 8 Portal vein.

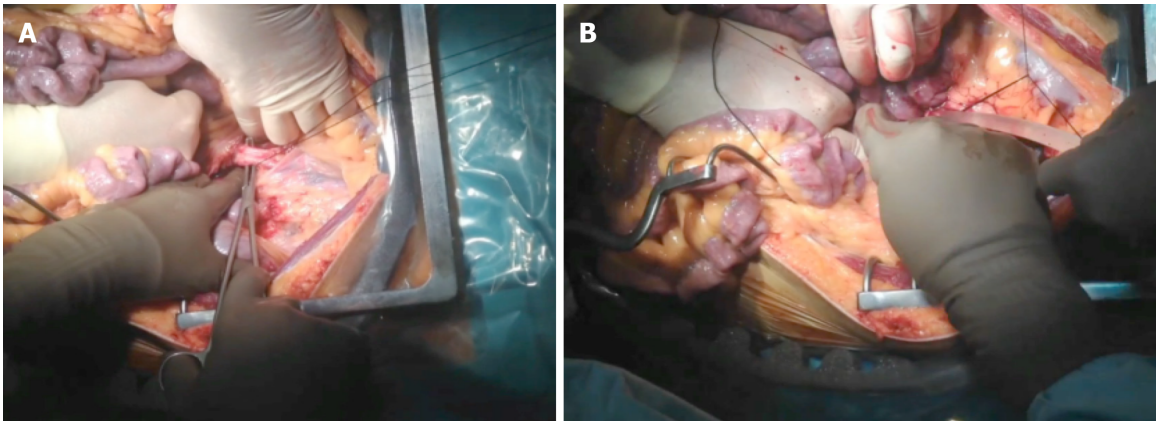

Figure 9 Aortic canula in super-fast retrieval. A and B: Intraoperative views of the procedure, showing different aspects. Photos provided by Dr Perez Daga, pancreas transplant surgeon (Malaga, Spain).

low blood flow in the pump due to the absence of venous return from the chest and head, 1-1.5 L of saline is perfused to the DCD just prior to vena cava ligation. The potential advantage is that it provides a continuous circulation that is able to improve the metabolic support during perfusion, preserving the microcirculation of the organs and thereby improving preservation. Another important aspect is that it allows the

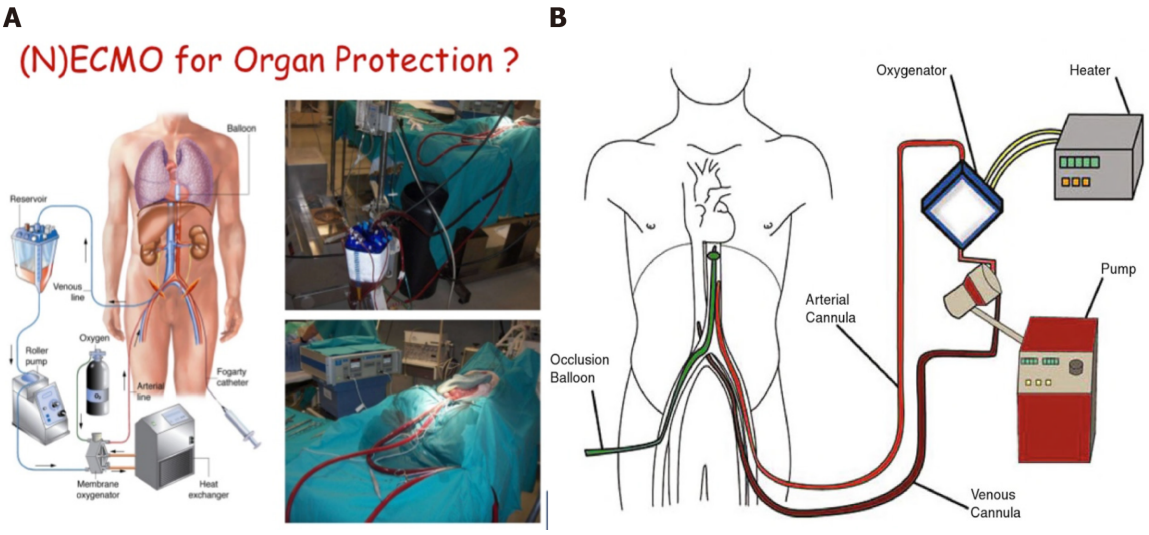

Figure 10 Normothermic circulation. A: Picture of normothermic preservation machines (NECMO); B: Diagram of NECMO. NECMO: Normothermic preservation machines.

quality of the organs to be evaluated before transplantation, especially in those organs coming from donors with expanded criteria. Finally, it reduces the risk of delayed graft function and improves the survival of the graft.

One of the complications related to the severe anticoagulation, to which these donors are subjected, is the risk of postoperative bleeding, along with the consequently required reoperation. Other complications observed include the existence of peripancreatic hematomas with risk of abdominal compartmental syndrome, especially with the use of a retroperitoneal graft technique. A compartment syndrome exists when increased pressure in a closed anatomic space threatens the viability of the tissue within the compartment[44-47]. In these cases, the entire wound must be opened to drain the hematoma and liberate the graft from the existing pressure, since otherwise the ischemia and thrombosis of the graft is the rule. Subsequently, a negative pressure closure technique is recommended (Figure 11).

Negative-pressure wound therapy is a frequently applied open abdomen treatment. There are only few experimental data published in support of this method and describing the optimal settings and pressure distribution in the abdominal cavity during this procedure[48-51]. The retrieval and preservation of the pancreas for transplantation is a surgical procedure that requires very high level anatomical and technical knowledge. It is necessary to remember that the pancreas is the most frequently discarded organ during donation.

CONCLUSION

Pancreas transplant is a milestone in the treatment of diabetes mellitus, for selected patients. Despite the improvement of its results in terms of patient and graft survival (similar to the transplantation of other solid organs), its complications are important and numerous, often compromising the viability of the transplant. For this reason, we must be very careful with the selection of donors and recipients, as well as with the technical aspects related to the retrieval, preservation and transplantation of the pancreas. The new techniques of retrieval and preservation of the pancreas in asystole donors have allowed us to increase the pool of donors while maintaining safety guidelines for patients.

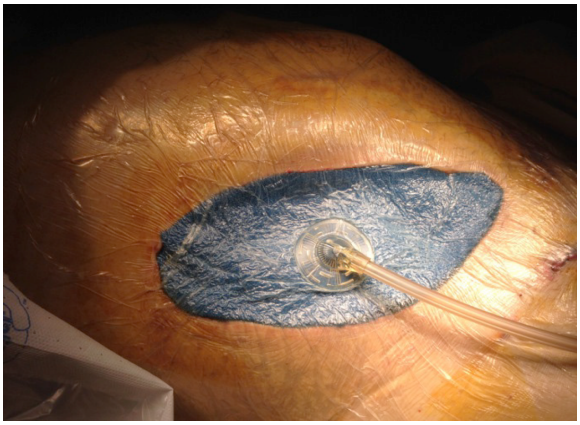

Figure 11 Negative-pressure wound therapy.

REFERENCES

1 **Krieger NR**, Odorico JS, Heisey DM, D'Alessandro AM, Knechtle SJ, Pirsch JD, Sollinger HW. Underutilization of pancreas donors. *Transplantation* 2003; **75**: 1271-1276 [PMID: 12717215 DOI: 10.1097/01.TP.0000061603.95572.BF]

2 **Lam HD**, Schaapherder AF, Kopp WH, Putter H, Braat AE, Baranski AG. Professionalization of surgical abdominal organ recovery leading to an increase in pancreatic allografts accepted for transplantation in the Netherlands: a serial analysis. *Transpl Int* 2017; **30**: 117-123 [PMID: 27874968 DOI: 10.1111/tri.12893]

3 **Wullstein C**, Woeste G, de Vries E, Persijn GG, Bechstein WO. Acceptance criteria of pancreas grafts: how do surgeons decide in Europe? *Transplant Proc* 2005; **37**: 1259-1261 [PMID: 15848688 DOI: 10.1016/j.transproceed.2004.12.146]

4 **Maglione M**, Ploeg RJ, Friend PJ. Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation. *Curr Opin Organ Transplant* 2013; **18**: 83-88 [PMID: 23254698 DOI: 10.1097/MOT.0b013e32835c29ef]

5 **Gruessner AC**, Sutherland DE, Gruessner RW. Pancreas transplantation in the United States: a review. *Curr Opin Organ Transplant* 2010; **15**: 93-101 [PMID: 20009932 DOI: 10.1097/MOT.0b013e32833552d2]

6 **Troppmann C**. Complications after pancreas transplantation. *Curr Opin Organ Transplant* 2010; **15**: 112-118 [PMID: 20009931 DOI: 10.1097/MOT.0b013e3283355349]

7 **Goodman J**, Becker YT. Pancreas surgical complications. *Curr Opin Organ Transplant* 2009; **14**: 85-89 [PMID: 19337152 DOI: 10.1097/MOT.0b013e328320a8ec]

8 **Humar A**, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AC, Sutherland DE. Technical failures after pancreas transplants: why grafts fail and the risk factors--a multivariate analysis. *Transplantation* 2004; **78**: 1188-1192 [PMID: 15502718 DOI: 10.1097/01.tp.0000137198.09182.a2]

9 **Brockmann JG**, Vaidya A, Reddy S, Friend PJ. Retrieval of abdominal organs for transplantation. *Br J Surg* 2006; **93**: 133-146 [PMID: 16432811 DOI: 10.1002/bjs.5228]

10 **Marsh CL**, Perkins JD, Sutherland DE, Corry RJ, Sterioff S. Combined hepatic and pancreaticoduodenal procurement for transplantation. *Surg Gynecol Obstet* 1989; **168**: 254-258 [PMID: 2645667]

11 **Dunn DL**, Morel P, Schlumpf R, Mayoral JL, Gillingham KJ, Moudry-Munns KC, Krom RA, Gruessner RW, Payne WD, Sutherland DE. Evidence that combined procurement of pancreas and liver grafts does not affect transplant outcome. *Transplantation* 1991; **51**: 150-157 [PMID: 1987684 DOI: 10.1097/00007890-199101000-00023]

12 **Sanseverino R**, Martin X, Caldara R, Faure JL, Lefrancois N, Dubernard JM. Technique of pancreas revascularization after combined liver and pancreas harvesting in the same cadaveric donor. *Clin Transplant* 1991; **5**: 55-59 [PMID: 10147635]

13 **Fridell JA**, Powelson JA, Kubal CA, Burke GW, Sageshima J, Rogers J, Stratta RJ. Retrieval of the pancreas allograft for whole-organ transplantation. *Clin Transplant* 2014; **28**: 1313-1330 [PMID: 25203627 DOI: 10.1111/ctr.12459]

14 **Fernández ED**, Schmid M, Schlosser K, Mauer D; Working Group of the Organ Procurement Central Region of the German Foundation for Organ Transplantation (DSO). Technical complications in organ procurement. *Transplant Proc* 2007; **39**: 2975-2976 [PMID: 18089303 DOI: 10.1016/j.transproceed.2007.07.092]

15 **Molmenti EP**, Klein AS, Henry ML. Procurement of liver and pancreas allografts in donors with replaced/accessory right hepatic arteries. *Transplantation* 2004; **78**: 770-771 [PMID: 15371686 DOI: 10.1097/01.tp.0000132785.96091.d9]

16 **Ames SA**, Kisthard JK, Smith JL, Piper JB, Corry RJ. Successful combined hepatic and pancreatic allograft retrieval in donors with a replaced right hepatic artery. *Surg Gynecol Obstet* 1991; **173**: 216-

222 [PMID: 1925883]
17 **Baranski AG**, Lam HD, Braat AE, Schaapherder AF. The dorsal pancreatic artery in pancreas procurement and transplantation: anatomical considerations and potential implications. *Clin Transplant* 2016; **30**: 1360-1364 [PMID: 27555344 DOI: 10.1111/ctr.12814]
18 **Marang-van de Mheen PJ**, Hilling DE, Dirkes MC, Baranski AG. Surgical injuries of pancreatic allografts during procurement. *Clin Transplant* 2011; **25**: 737-743 [PMID: 20973826 DOI: 10.1111/j.1399-0012.2010.01335.x]
19 **Fridell JA,** Powelson JA, Sanders CE, Ciancio G, Burke GW 3rd, Stratta RJ. Preparation of the pancreas allograft for transplantation. *Clin Transplant* 2011; **25**: E103-E112 [PMID: 21362047 DOI: 10.1111/j.1399-0012.2011.01414.x]
20 **Wright FH**, Wright C, Ames SA, Smith JL, Corry RJ. Pancreatic allograft thrombosis: donor and retrieval factors and early postperfusion graft function. *Transplant Proc* 1990; **22**: 439-441 [PMID: 1691538]
21 **Humar A**, Kandaswamy R, Drangstveit MB, Parr E, Gruessner AG, Sutherland DE. Prolonged preservation increases surgical complications after pancreas transplants. *Surgery* 2000; **127**: 545-551 [PMID: 10819063 DOI: 10.1067/msy.2000.104742]
22 **Sollinger HW**, Vernon WB, D'Alessandro AM, Kalayoglu M, Stratta RJ, Belzer FO. Combined liver and pancreas procurement with Belzer-UW solution. *Surgery* 1989; **106**: 685-690; discussion 690 [PMID: 2799643]
23 **Boggi U**, Vistoli F, Del Chiaro M, Signori S, Croce C, Pietrabissa A, Berchiolli R, Marchetti P, Del Prato S, Mosca F. Pancreas preservation with University of Wisconsin and Celsior solutions: a single-center, prospective, randomized pilot study. *Transplantation* 2004; **77**: 1186-1190 [PMID: 15114082 DOI: 10.1097/01.tp.0000120535.89925.ca]
24 **Parsons RF**, Guarrera JV. Preservation solutions for static cold storage of abdominal allografts: which is best? *Curr Opin Organ Transplant* 2014; **19**: 100-107 [PMID: 24553501 DOI: 10.1097/MOT.0000000000000063]
25 **Voigt MR**, DeLario GT. Perspectives on abdominal organ preservation solutions: a comparative literature review. *Prog Transplant* 2013; **23**: 383-391 [PMID: 24311404 DOI: 10.7182/pit2013100]
26 **Potdar S**, Malek S, Eghtesad B, Shapiro R, Basu A, Patel K, Broznick B, Fung J. Initial experience using histidine-tryptophan-ketoglutarate solution in clinical pancreas transplantation. *Clin Transplant* 2004; **18**: 661-665 [PMID: 15516240 DOI: 10.1111/j.1399-0012.2004.00262.x]
27 **Agarwal A**, Powelson JA, Goggins WC, Milgrom ML, Fridell JA. Organ preservation with histidine-tryptophan ketogluatarate solution in clinical pancreas transplantation: an update of the indiana university experience. *Transplant Proc* 2008; **40**: 498-501 [PMID: 18374113 DOI: 10.1016/j.transproceed.2008.01.011]
28 **Baertschiger RM,** Berney T, Morel P. Organ preservation in pancreas and islet transplantation. *Curr Opin Organ Transplant* 2008; **13**: 59-66 [PMID: 18660708 DOI: 10.1097/MOT.0b013e3282f44a63]
29 **Muthusamy AS**, Mumford L, Hudson A, Fuggle SV, Friend PJ. Pancreas transplantation from donors after circulatory death from the United Kingdom. *Am J Transplant* 2012; **12**: 2150-2156 [PMID: 22845910 DOI: 10.1111/j.1600-6143.2012.04075.x]
30 **Qureshi MS,** Callaghan CJ, Bradley JA, Watson CJ, Pettigrew GJ. Outcomes of simultaneous pancreas-kidney transplantation from brain-dead and controlled circulatory death donors. *Br J Surg* 2012; **99**: 831-838 [PMID: 22437616 DOI: 10.1002/bjs.8733]
31 **Salvalaggio PR,** Davies DB, Fernandez LA, Kaufman DB. Outcomes of pancreas transplantation in the United States using cardiac-death donors. *Am J Transplant* 2006; **6**: 1059-1065 [PMID: 16611344 DOI: 10.1111/j.1600-6143.2006.01310.x]
32 **Fernandez LA,** Di Carlo A, Odorico JS, Leverson GE, Shames BD, Becker YT, Chin LT, Pirsch JD, Knechtle SJ, Foley DP, Sollinger HW, D'Alessandro AM. Simultaneous pancreas-kidney transplantation from donation after cardiac death: successful long-term outcomes. *Ann Surg* 2005; **242**: 716-723 [PMID: 16244546 DOI: 10.1097/01.sla.0000186175.84788.50]
33 **Boggi U,** Vistoli F, Del Chiaro M, Signori S, Pietrabissa A, Costa A, Bartolo TV, Catalano G, Marchetti P, Del Prato S, Rizzo G, Jovine E, Pinna AD, Filipponi F, Mosca F. A simplified technique for the en bloc procurement of abdominal organs that is suitable for pancreas and small-bowel transplantation. *Surgery* 2004; **135**: 629-641 [PMID: 15179369 DOI: 10.1016/j.surg.2003.10.011]
34 **Jeon H,** Ortiz JA, Manzarbeitia CY, Alvarez SC, Sutherland DE, Reich DJ. Combined liver and pancreas procurement from a controlled non-heart-beating donor with aberrant hepatic arterial anatomy. *Transplantation* 2002; **74**: 1636-1639 [PMID: 12490801 DOI: 10.1097/00007890-200212150-00025]
35 **de Boer JD,** Kopp WH, Ooms K, Haase-Kromwijk BJ, Krikke C, de Jonge J, van Heurn LW, Baranski AG, van der Vliet JA, Braat AE. Abdominal organ procurement in the Netherlands - an analysis of quality and clinical impact. *Transpl Int* 2017; **30**: 288-294 [PMID: 27992973 DOI: 10.1111/tri.12906]
36 **Reich DJ,** Mulligan DC, Abt PL, Pruett TL, Abecassis MM, D'Alessandro A, Pomfret EA, Freeman RB, Markmann JF, Hanto DW, Matas AJ, Roberts JP, Merion RM, Klintmalm GB; ASTS Standards on Organ Transplantation Committee. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant* 2009; **9**: 2004-2011 [PMID: 19624569 DOI: 10.1111/j.1600-6143.2009.02739.x]
37 **Hessheimer AJ,** Billault C, Barrou B, Fondevila C. Hypothermic or normothermic abdominal regional perfusion in high-risk donors with extended warm ischemia times: impact on outcomes?

Transpl Int 2015; **28**: 700-707 [PMID: 24797796 DOI: 10.1111/tri.12344]

38 **Miñambres E,** Rubio JJ, Coll E, Domínguez-Gil B. Donation after circulatory death and its expansion in Spain. *Curr Opin Organ Transplant* 2018; **23**: 120-129 [PMID: 29120882 DOI: 10.1097/MOT.0000000000000480]

39 **Brogi E**, Circelli A, Gamberini E, Russo E, Benni M, Pizzilli G, Agnoletti V. Normothermic Regional Perfusion for Controlled Donation After Circulatory Death: A Technical Complication During Normothermic Regional Perfusion. *ASAIO J* 2020; **66**: e19-e21 [PMID: 31085950 DOI: 10.1097/MAT.0000000000000963]

40 **Oniscu GC,** Randle LV, Muiesan P, Butler AJ, Currie IS, Perera MT, Forsythe JL, Watson CJ. In situ normothermic regional perfusion for controlled donation after circulatory death--the United Kingdom experience. *Am J Transplant* 2014; **14**: 2846-2854 [PMID: 25283987 DOI: 10.1111/ajt.12927]

41 **Barlow AD,** Hosgood SA, Nicholson ML. Current state of pancreas preservation and implications for DCD pancreas transplantation. *Transplantation* 2013; **95**: 1419-1424 [PMID: 23579769 DOI: 10.1097/TP.0b013e318285558f]

42 **Miñambres E,** Suberviola B, Dominguez-Gil B, Rodrigo E, Ruiz-San Millan JC, Rodríguez-San Juan JC, Ballesteros MA. Improving the Outcomes of Organs Obtained From Controlled Donation After Circulatory Death Donors Using Abdominal Normothermic Regional Perfusion. *Am J Transplant* 2017; **17**: 2165-2172 [PMID: 28141909 DOI: 10.1111/ajt.14214]

43 **Butler AJ,** Randle LV, Watson CJ. Normothermic regional perfusion for donation after circulatory death without prior heparinization. *Transplantation* 2014; **97**: 1272-1278 [PMID: 24646774 DOI: 10.1097/TP.0000000000000082]

44 44 Pineda-Solís K, Xie WY, McAlister V, Sener A, Luke PP. Retroperitoneal Compartment Syndrome in Renal Transplantation: How to Salvage the Graft? Urology 2017; 107: 268 [PMID: 28982622 DOI: 10.1016/j.urology.2017.05.015]

45 **Ortiz J,** Parsikia A, Horrow MM, Khanmoradi K, Campos S, Zaki R. Risk factors for renal allograft compartment syndrome. *Int Surg* 2014; **99**: 851-856 [PMID: 25437599 DOI: 10.9738/INTSURG-D-13-00214.1]

46 **Handschin AE**, Weber M, Renner E, Clavien PA. Abdominal compartment syndrome after liver transplantation. *Liver Transpl* 2005; **11**: 98-100 [PMID: 15690542 DOI: 10.1002/Lt.20295]

47 **Michalska M,** Wen K, Pauly RP. Acute Kidney Injury in Pregnant Patient With Pancreas-Kidney Transplant Caused by Abdominal Compartment Syndrome: A Case Presentation, Review of Literature, and Proposal of Diagnostic Approach. *Can J Kidney Health Dis* 2019; **6**: 2054358119861942 [PMID: 31384476 DOI: 10.1177/2054358119861942]

48 **Wang TY,** Elliott R, Low DW. Damage control abdomen: single-stage reconstruction using a vicryl mesh buttress. *Ann Plast Surg* 2013; **70**: 324-330 [PMID: 22791067 DOI: 10.1097/SAP.0b013e3182361af9]

49 **Ghazi B**, Deigni O, Yezhelyev M, Losken A. Current options in the management of complex abdominal wall defects. *Ann Plast Surg* 2011; **66**: 488-492 [PMID: 21372667 DOI: 10.1097/SAP.0b013e31820d18db]

50 **Smith CT,** Katz MG, Foley D, Welch B, Leverson GE, Funk LM, Greenberg JA. Incidence and risk factors of incisional hernia formation following abdominal organ transplantation. *Surg Endosc* 2015; **29**: 398-404 [PMID: 25125093 DOI: 10.1007/s00464-014-3682-8]

51 **Huang C**, Leavitt T, Bayer LR, Orgill DP. Effect of negative pressure wound therapy on wound healing. *Curr Probl Surg* 2014; **51**: 301-331 [PMID: 24935079 DOI: 10.1067/j.cpsurg.2014.04.001]

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MINIREVIEWS

Exocrine drainage in pancreas transplantation: Complications and management

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Abstract

The aim of this minireview is to compare various pancreas transplantation exocrine drainage techniques *i.e.*, bladder *vs* enteric. Both techniques have different difficulties and complications. Numerous comparisons have been made in the literature between exocrine drainage techniques throughout the history of pancreas transplantation, detailing complications and their impact on graft and patient survival. Specific emphasis has been made on the early postoperative management of these complications and the related surgical infections and their consequences. In light of the results, a number of bladder-drained pancreas grafts required conversion to enteric drainage. As a result of technical improvements, outcomes of the varied enteric exocrine drainage techniques (duodeno-jejunostomy, duodenoduodenostomy or gastric drainage) have also been discussed *i.e.*, assessing specific risks *vs* benefits. Pancreatic exocrine secretions can be drained to the urinary or intestinal tracts. Until the late 1990s the bladder drainage technique was used in the majority of transplant centers due to ease of monitoring urine amylase and lipase levels for evaluation of possible rejection. Moreover, bladder drainage was associated at that time with fewer surgical complications, which in contrast to enteric drainage, could be managed with conservative therapies. Nowadays, the most commonly used technique for proper driving of exocrine pancreatic secretions is enteric drainage due to the high rate of urological and metabolic complications associated with bladder drainage. Of note, 10% to 40% of bladder-drained pancreata eventually required enteric conversion at no detriment to overall graft survival. Various surgical techniques were originally described using the small bowel for enteric anastomosis with Roux-en-

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Y loop or a direct side-to-side anastomosis. Despite the improvements in surgery, enteric drainage complication rates ranging from 2%-20% have been reported. Treatment depends on the presence of any associated complications and the condition of the patient. Intra-abdominal infection represents a potentially very serious problem. Up to 30% of deep wound infections are associated with an anastomotic leak. They can lead not only to high rates of graft loss, but also to substantial mortality. New modifications of established techniques are being developed, such as gastric or duodenal exocrine drainage. Duodeno-duodenostomy is an interesting option, in which the pancreas is placed behind the right colon and is oriented cephalad. The main concern of this technique is the challenge of repairing the native duodenum when allograft pancreatectomy is necessary. Identification and prevention of technical failure remains the main objective for pancreas transplantation surgeons. In conclusion, despite numerous techniques to minimize exocrine pancreatic drainage complications *e.g.*, leakage and infection, no universal technique has been standardized. A prospective study/registry analysis may resolve this.

Key Words: Graft survival; Patient survival; Anastomotic leak; Morbidity; Infection; Surgery

Core Tip: A review of recent post-transplant complications regarding bladder drainage (urologic complications), enteric drainage (leak), surgical infections and abdominal compartment syndrome. Although safe and effective, bladder drainage brings metabolic and urologic complications; therefore, physiologic enteric drainage is preferred. Nevertheless, intra-abdominal infections and laparotomies arising from complications may result in significant graft loss. New modifications of established techniques are being developed, such as gastric or duodenal exocrine drainage. Donor-related factors, preservation injury, and surgical techniques should be managed to minimize adverse post-transplant events.

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INTRODUCTION

The first successful human pancreas transplant was performed on December 17, 1966 at the University of Minnesota[1]. Since then, a variety of pancreas transplant surgical techniques have evolved, as is evident from the wide ranging contributions provided by transplant groups throughout the world[2,3]. Regarding exocrine pancreas drainage, outcomes have improved notably since the first physiologic enteric procedures designed to divert pancreatic ductal secretions. Previously, drainage of exocrine secretions was *via* the gut or in the urinary bladder. The bladder drainage (BD) technique was used in most transplant centers until the late 1990s[3]. The duodenocystostomy contributed extraordinarily to the viability of pancreas transplants, as it allowed monitoring of pancreatic allograft function *via* urinary amylase measurements together with directed biopsy of duodenal mucosa and/or pancreas graft by cystoscopy[4-6] . Moreover, BD was associated at that time with fewer surgical complications when compared with enteric drainage[3]. However, this approach brings with it morbidity since it creates a nonphysiologic condition from which specific metabolic and urologic complications may arise. As a result of these common complications, the majority of centers now utilize enteric drainage, currently considered the optimal method in the management of pancreatic exocrine secretions[7]. Given the success of the enteric drainage, limited progress has thus been made in the field of BD in terms of novel surgical approaches. Notwithstanding, BD is still a

considered alternative in selected cases when allograft duodenum viability is doubtful due to reperfusion injury, or an increased likelihood of acute rejection in the case of solitary pancreas transplantation[7].

Taking into account the historic importance of BD in pancreas transplantation, and because it remains a preferred option at specific centers, some immediate post-operative complications have been outlined below.

BLADDER DRAINAGE

Using this technique, the graft duodenum is, in effect an exocrine conduit and is anastomosed to the bladder by the classic double-layer hand sewn technique (Figure 1) or using a circular stapler[8,9].

Consequently, metabolic issues arise from urinary loss of pancreatic juice, together with its alkaline content. In spite of most patients compensating with increased hydration and bicarbonate supplementation, hyperchloremic metabolic acidosis and dehydration may occur[6]. In an attempt to minimize protein and bicarbonate loss from the allograft duodenal mucosa, the length of donor duodenum transplanted with the pancreas has been progressively shortened over time[7].

In addition, urologic complications have been reported in the literature[6,10-18] including: Hematuria (16%); duodenal segment leaks (14%); reflux pancreatitis (11%); recurrent urinary tract infections (10%); urethritis (3%); and urethral stricture/disruption (3%). Also, abnormal pre-transplant urodynamic tests may increase the incidence of urologic complications[19]. Despite the high incidence of urologic complications, the patient and graft survival rates are not affected[3].

Regarding *vesical bleeding, early post-transplant hematuria* is frequent and is usually self-limited. This development is due to bladder surgical manipulation in addition to duodenal mucosal bleeding. In some recipients, with severe postoperative hematuria, management includes the institution of a continuous bladder irrigation regimen. If bleeding persists, cystoscopy is needed.

In contrast to enteric drainage, bladder drainage does not interfere with native bowel integrity. Consequently, *graft leaks* related to the latter generally have a decreased rate of life-threatening infectious complications and a less serious clinical course[3,7]. *Nascent leaks* (≤ 4 wk post-transplant) typically occur at the duodeno-cystostomy; while *later leaks* (> 4 wk post-transplant) usually originate from the donor duodenum, in some cases from the lateral duodenal staple line or when caused by ulcers, from the general area of the duodenal segment[18,20-21]. Initially, postoperative patients may complain of abdominal discomfort, or an asymptomatic rise in pancreatic enzymes may occur. Furthermore, urine production may decrease and serum creatinine levels may increase, although symptoms usually improve after Foley catheter placement. Low-pressure cystography or abdominal computed tomography (CT) with retrograde bladder contrast is used in the diagnosis of bladder-drained graft leaks. Extended bladder decompression is the treatment usually employed. This involves Foley catheterization together with percutaneous drainage of associated intraabdominal fluid collections (nascent leaks). High volume or infected postoperative leakage in bladder-drained recipients exhibiting peritonitis may need relaparotomy and surgical repair. In the case of significant compromise of the duodenal stump, a transplant pancreatectomy should be considered. Late-onset duodenocystostomy/duodenal segment leaks typically call for conversion from bladder to enteric drainage, regardless of etiology[21].

Sollinger *et al*[18] previously described a condition known as *reflux pancreatitis*, defined by the following criteria: (1) Rapid onset of lower abdominal pain situated around the pancreatic graft; (2) Increased serum amylase; (3) No leakage; (4) Pancreas edema, without evidence of abscess/fluid collection on computed tomography scan; and (5) 24 h resolution of symptoms following Foley catheter placement. Graft pancreatitis is most likely caused by reflux of urine into the pancreatic duct during the micturition high-pressure phase, when detrusor pressures exceed those existing in the pancreatic duct (10-12 cm water)[13,22]. Stephanian *et al*[23] speculated that this process may be exacerbated by sphincter of Oddi incompetence or through stagnation of exocrine secretions in a neuropathic bladder. As suggested by Fernandez-Cruz *et al*[24] the Oddi sphincter may be occluded secondary to rejection, and may result in enzyme release and graft pancreatitis. It has been reported that obstruction arising from calculous formation in the duodenal segment, could result in reflux pancreatitis[25]. Repeated episodes of reflux pancreatitis are possible, but in these cases an intensive search for a small leak has to be initiated. Therapy consisting of Foley drainage for

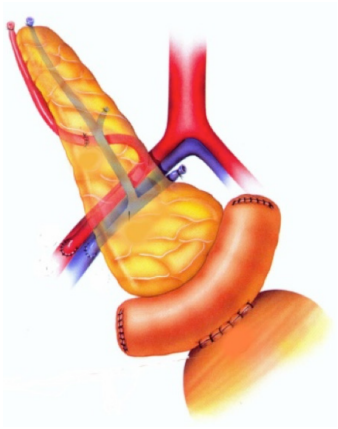

Figure 1 Whole-organ transplant with systemic vein and bladder exocrine drainage. The pancreas is placed intraabdominally, on the right side of the pelvis. Anastomosis between the graft duodenal segment and vesical dome of the recipient bladder is performed. Image courtesy of Prof. Fernández-Cruz.

several days is usually successful[18]. Antibiotics are indicated if urinary tract infection is present[26].

In diabetic patients, *urinary tract infections* are common, although most of these respond to appropriate antibiotic management. Contributing factors include prolonged catheter drainage, alkaline urine secondary to bicarbonate excretion from the exocrine pancreas, mucosal damage, and the presence of a diabetic neuropathic bladder with incomplete emptying[18]. Moreover, it has been previously documented that non-absorbable sutures and staples can be a focus for urinary calculi in bladder-drained pancreas transplantation[27]. Persistent urinary tract infections call for further study, such as cystoscopic examination with the view to excluding underlying lower urinary tract pathologies.

Other specific complications of BD such as *urethritis, urethral strictures, and disruptions,* are most likely due to activation of pancreatic enzymes in the bladder. It was speculated that a higher content of trypsinogen in the pancreatic secretions of certain recipients is responsible for this complication[18]. Despite urethral complications being largely restricted to male patients, they could also present in females[23]. They are initially manifested by pain and discomfort during urination. Initial conservative treatment consists of placement of a Foley catheter for several weeks. If symptoms recur, urethrogram and/or cystoscopy should be performed. Disruptions of the urethra with massive extravasation will respond with complete resolution after enteric drainage. Due to the above complications, conversion from bladder to enteric drainage may be deemed necessary[28-31]. The reported conversion rate from BD to enteric drainage ranges from 10% to 40%[28-38].

A recent study by Riad *et al*[39] looked into the link between enteric conversion and the resulting pancreas graft and patient outcomes by analyzing 593 recipients with bladder-drained pancreata, the majority of which received solitary transplants and 70 received simultaneous pancreas-kidney transplants. It was concluded that enteric conversion was associated with increased risk of rejection, but not graft loss or mortality. A longer interval from engraftment to conversion appears favorable. In addition, in a University of Wisconsin study[30], some 162 (41.9%) out of 386 bladder-drained pancreata eventually required enteric conversion, 29 (17.9%) within the first year, and without affecting the overall graft survival. In this series, there were no known exocrine content leaks, and the majority of the post-conversion surgical complications were managed conservatively or *via* percutaneous measures. Regrettably, in this setting, serious morbidity can occur[39] and consequently management of surgical complications can be challenging. In the case of enterovesical fistula formation described elsewhere[5,40], various options can be considered, including: Constructing a Roux-en-Y duodeno-enteric anastomosis in addition to bladder repair; donor duodenum-bladder reconnection, including resection and reanastomosis of the small bowel segment involved; or to perform a graft pancreatectomy. However, it is important to keep in mind that some factors (patient immunosuppressed status, the increased possibility of local contamination, and the elevated risk of duodenal segment ischemia) increase the surgical management failure rate, resulting in a graft pancreatectomy. All attempts should therefore be made to treat these patients conservatively.

ENTERIC DRAINAGE

Various technical contributions in the search for the perfect technique for endogenous replacement of beta cell function and proper driving of exocrine secretions have been proposed. Despite leaks from the allograft duodenum having been reported in 5%-20% of bladder-drained and 5%-8% of bowel-drained pancreas transplants[41-43], some studies have shown no consistent differences in outcomes for bladder-drained or enteric-drained pancreas transplants with either portal or systemic venous drainage. In the modern era, pancreas transplantation with primary enteric exocrine drainage and systemic or portal venous anastomosis is performed in most cases[44]. A variety of techniques have been described using different small bowel sites for the enteric anastomosis[7,45]. Some groups prefer to use a Roux-en Y loop, while other surgeons choose direct anastomosis[2] (Figure 2). Most commonly, the duodenum-jejunum anastomosis is performed using a 2-layer, hand-sewn technique to create a hemostatic closure[46]. Although bleeding rates may be higher, techniques using either the circular or linear stapler were also described with the view to simplifying enteric anastomosis[47,48].

Newer techniques include drainage into native duodenum[49,50] and stomach[51]. Theoretically, the duodenoduodenostomy technique (Figure 3) (side-to-side anastomosis between the duodenal segment and the lower knee of the recipients' duodenum with a 2.5- to 3.0-cm longitudinal duodenotomy) could facilitate intervention such as stenting of the pancreatic duct in cases of exocrine leakage among other advantages such as facilitating endoscopic access to the site of exocrine drainage for biopsies of the pancreas graft, when indicated[50].

The well tolerated gastric drainage procedure provides excellent patient and graft survival[3] as the third portion of the donor duodenum is anastomosed in two layers to the greater curvature of the stomach. Access to graft duodenum and pancreas *via* endoscopy is novel and straightforward[51].

A multitude of variations have arisen in the search for the ideal technique to address the problems associated with the management of pancreatic exocrine secretions. With increasing experience, the incidence of postoperative complications[3,52] (2%-10%) has notably reduced in recent years, with less than 1% of grafts lost due to this cause.

However, *enteric leakage* continues to be a significant source of morbidity[53]. Fistulas arising in the 3 mo following surgery are typically a result of ischemia or technical issues, while later fistulas usually arise from infections or acute rejection. This event represents the second cause of relaparotomy following hemorrhage[21].

Enteric leakage usually shares signs and symptoms characteristic of intestinal perforation, including abdominal pain, fever, nausea and vomiting, tachycardia, leukocytosis, peritonitis, or sepsis[53]. In unclear cases, radiographic imaging often provides confirmatory evidence, with CT imaging with oral contrast being the most useful. Findings may comprise intraperitoneal fluid, extraluminal air, and contrast extravasation[54].

Resulting treatment depends on the type of exocrine secretion derivation and the severity of the leak. In the present setting, early enteric leakage almost always requires relaparotomy with an anastomotic revision, with treatment depending on leakage extent and graft duodenum condition. When anastomosis is performed between the *graft duodenum and the recipient jejunum*, simple oversewing may be sufficient for small leaks with limited abdominal contamination in a patient hemodynamically stable. In the patient with a leak located adjacent to a staple line, performing a repair by limited duodenal resection with a GIA stapler could be indicated. Should part of the duodenum be compromised, the portion in question may be resected and the remaining duodenum shortened. If the original anastomosis has been performed in a side-to-side fashion, a Roux-en-Y limb may be created with the aim of diverting the intestinal stream away from the graft[53]. A total duodenectomy offers another management approach for duodenal leaks[55-57]. Having said this, these procedures are generally reserved for stable patients with limited abdominal contamination. On rare occasions, pancreatic head resection and subsequent duct-to-intestine anastomosis may be performed[58]. A graft pancreatectomy is the preferred choice in cases of: Significant leakage with sepsis or severe peritonitis; the presence of devitalized tissue; patient instability[59]. In one of the largest single-centre series, Sollinger *et al*[33], described a leakage rate of 5.7% in 610 enterically drained transplants, of which up to 50% resulted in pancreas graft loss. No consistent reports demonstrated the benefit of using octreotide in drained patients to promote fistula closure[60,61].

Interestingly, in 2005, Boggi *et al*[62] described a modified technique with portal-enteric drainage performed *via* a transperitoneal approach, with the pancreas graft

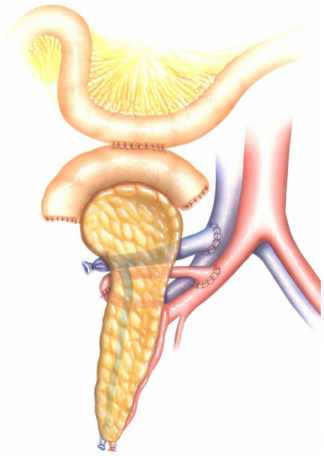

Figure 2 Whole-organ transplant with systemic vein and enteric exocrine drainage (cephalad position). A two-layer side-to-side duodenojejunostomy is constructed about 40-80 cm distal to the ligament of Treitz. Image courtesy of Prof. Fernández-Cruz.

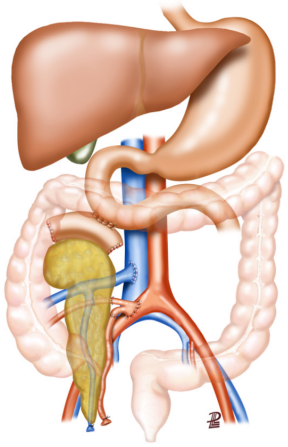

Figure 3 Whole-organ transplant with systemic vein and enteric exocrine drainage (cephalad position). Duodenoduodenostomy technique with side-to-side anastomosis between the duodenal segment and the lower knee of the recipient´s duodenum. Image courtesy of Prof. García-Valdecasas.

placed into a fully retroperitoneal position. A duodenojejunostomy was performed side-by-side together with a Roux-en-Y jejunal limb. An advantage of "retroperitoneal" graft location behind the right colon is that, instead of causing peritonitis, potentially septic complications remain localized as peripancreatic fluid collections. In view of this, other surgeons have adopted this technique, employing a systemic venous drainage in the inferior vena cava[63,64].

Similarly, when duodenoduodenostomy is performed, the pancreas allograft is inserted vertically with the head upright and placed in a retrocolic position, behind the recipient´s bowel. In selected cases, this method can facilitate conservative management of an enteric leak, largely due to a decreased likelihood of intraperitoneal contamination. In allograft pancreatectomies, concerns persist regarding the safety of these maneuvers in the setting of local inflammation/sepsis in spite of recommendations for closure of the opening on the native duodenum[3]. Lindah *et al*[50], assessed safety profiles with duodenoduodenostomy *vs* duodenojejunostomy procedures. The percentage of anastomotic leakage was 5% and 4%, respectively. When a pancreatectomy is needed, adequate mobilization of the duodenum is mandatory with the aim of achieving a tension-free closure. To avoid stenosis the hole is closed transversely to the longitudinal duodenotomy using a single full-layer absorbable synthetic monofilament 4-0 suture (*e.g.*, Biosyn, MonoPlus). There has been no need for duodenal exclusion or gastrectomy. In the series published by Walter *et al*[65], anastomotic insufficiency (1.6% *vs* 7%) and relaparotomy (41% *vs* 48%) occurred more frequently in the duodenojejunostomy group, whereas gastrointestinal bleeding (11% *vs* 3%) occurred more often in the duodenoduodenostomy group. The resulting hole in the recipient duodenum was, in all cases, initially treated using a

transverse, two-layer, interrupted polydioxanone (3-0 or 4-0) suture. Following pancreatectomy and duodenum oversewing, three patients developed duodenal suture insufficiencies with consecutive duodenal leak, treated with a Roux-en-Y duodenojejunostomy, forming a side-to-side anastomosis. The third patient was treated conservatively with a longer-term intra-abdominal drain.

Currently, duodenoduodenostomy is a feasible and safe method *i.e.*, equivalent to other classic techniques, extending the viability of anastomotic sites, especially in the case of re-transplanted recipients.

In an attempt to minimize early bowel leaks, special attention should be paid to the detection and control of potential risk factors for both donor and recipient *i.e.* those arising from donor hemodynamic instability, ischemia-reperfusion and preservation trauma (preservation solution/warm-cold ischemia), back-table preparation of the graft or other technical issues[21].

As demonstrated, leaks continue to be a persistent issue, especially as they represent a significant risk factor for *intraabdominal abscesses*, a third of which are associated with an anastomotic leak (duodenoenterostomy or duodenocystostomy)[21]. Infections are frequent in this group of transplant recipients, playing a central role in patient and graft survival, with diabetes, surgery, and immunosuppression as predisposing factors. Consistent with other studies reporting a proportion of patients affected by bacterial infections ranging from 51% to 95%[66-68], Bodro *et al*[69] demonstrated urinary tract infection as the most frequent (61%), followed by abdominal and surgical site infection.

Intra-abdominal infections represent a potentially serious problem, leading to not only high rates of graft loss, but substantial mortality[21,70]. Infections usually occur within 30 days of transplant, with bacterial etiology being more common than fungal abscesses. Intraabdominal infection risk factors comprise: Older donor age; retransplantation; pre-transplant peritoneal dialysis; extended preservation time; graft pancreatitis; and immunosuppression with sirolimus[21,71,72].

As treatment largely depends on the infection type (diffuse peritonitis *vs* localized abscess) any diagnostic processes must detail both the extent and nature of any infection. Equally, other vascular and intestinal complications must be ruled out. The clinical presentation of intra-abdominal infection is similar (and closely related) to enteric leakage. Abdominal CT with oral and *iv* contrast (for bladder-drained grafts, and retrograde bladder contrast also used to rule out leakage from the duodenovesical anastomosis) is the preferred choice for diagnosis.

Associated complications and the condition of the patient notably affect treatment decisions. A stable patient with a localized abscess can generally be treated with percutaneous fluid drainage. Relaparotomy is mandatory should conservative treatment fail, patients develop widespread infection, or recipients deteriorate or become clinically unstable[70]. Ideally, cultures are recommended in order to determine appropriate antimicrobial therapy. It should be noted that intra-abdominal infection might predispose to pseudoaneurysm, more so when in close proximity to the vascular anastomosis[53].

Moreover, a *cytomegalovirus* (CMV) infection risk of approximately 15% exists, mostly as a result of potent antilymphocyte drugs. CMV infection is often associated with increases in mortality, rejection rates, and late duodenal leaks[73]. Prophylaxis schemes (against bacterial, viral, and fungal infections), established from the moment of intervention by the transplant groups, have managed to reduce its incidence in the short term.

Although there is a lack of reported cases in the literature concerning abdominal compartment syndrome (ACS) in pancreas transplantation, aspects of abdominal compartment mechanics have been depicted in some publications regarding liver transplant and hepato-biliary-pancreatic (HBP) surgery[74-76]. Systemic inflammatory response syndrome and the toll of surgical trauma promote ACS, leading to renal and respiratory failure in addition to other risk factors[77]. The World Society of ACS defines intra-abdominal hypertension (IAH) as a sustained or repeated pathological elevation of intra-abdominal pressure (IAP) of 12 mmHg[78]. In these cases, raised IAH levels act to exacerbate decreases in visceral perfusion in hypotensive patients with visceral vasoconstriction[79].

IAH is especially worrying in cases of severe acute pancreatitis and for patients with post-operative abdominal morbidity. IAP monitoring is indicated for gravely ill patients, with management ideally following general principles and standard recommendations of other cases. Factors such as adequate analgesia, neuromuscular blockade and mechanical ventilation may promote abdominal compliance. Gastrointestinal distension can be mitigated through the use of promotility agents and nasogastric and colonic decompression. In refractory cases, drainage of intra-

abdominal fluid collections is the initial invasive procedure to consider[80]. Negative pressure wound therapy has also been shown to be a safe treatment and can increase the chance for early fascial closure in septic patients. However, few data are available regarding the specific setting of transplantation[81].

As happens in other surgical scenarios, the implementation of robotic technology shows promise in the sense that it could decrease complications rates, thus improving the postoperative course of pancreas transplantation. Further study in this field is required to determine to what extent robotic pancreas transplantation could be beneficial for diabetic patients requiring beta-cell replacement[82-84].

CONCLUSION

Nowadays, the most commonly used technique for proper driving of exocrine pancreatic secretions is enteric drainage due to the high rate of urological and metabolic complications associated with bladder drainage. Despite numerous techniques to minimize exocrine pancreatic drainage complications *e.g.*, leakage and infection, no universal technique has been standardized. A prospective study or large registry analysis may resolve this controversy.

REFERENCES

1 **Kelly WD**, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery* 1967; **61**: 827-837 [PMID: 5338113]

2 **Di Carlo V**, Castoldi R, Cristallo M, Ferrari G, Socci C, Baldi A, Molteni B, Secchi A, Pozza G. Techniques of pancreas transplantation through the world: an IPITA Center survey. *Transplant Proc* 1998; **30**: 231-241 [PMID: 9532012 DOI: 10.1016/s0041-1345(98)00003-7]

3 **Laftavi MR**, Gruessner A, Gruessner R. Surgery of pancreas transplantation. *Curr Opin Organ Transplant* 2017; **22**: 389-397 [PMID: 28682797 DOI: 10.1097/MOT.0000000000000434]

4 **Sutherland DE**, Gruessner RW, Gruessner AC. Pancreas transplantation for treatment of diabetes mellitus. *World J Surg* 2001; **25**: 487-496 [PMID: 11344403 DOI: 10.1007/s002680020342]

5 **West M**, Gruessner AC, Metrakos P, Sutherland DE, Gruessner RW. Conversion from bladder to enteric drainage after pancreaticoduodenal transplantations. *Surgery* 1998; **124**: 883-893 [PMID: 9823403 DOI: 10.1016/S0039-6060(98)70013-3]

6 **Sollinger HW**, Odorico JS, Knechtle SJ, D'Alessandro AM, Kalayoglu M, Pirsch JD. Experience with 500 simultaneous pancreas-kidney transplants. *Ann Surg* 1998; **228**: 284-296 [PMID: 9742912 DOI: 10.1097/00000658-199809000-00002]

7 **El-Hennawy H**, Stratta RJ, Smith F. Exocrine drainage in vascularized pancreas transplantation in the new millennium. *World J Transplant* 2016; **6**: 255-271 [PMID: 27358771 DOI: 10.5500/wjt.v6.i2.255]

8 **Pescovitz MD**, Dunn DL, Sutherland DE. Use of the circular stapler in construction of the duodenoneocystostomy for drainage into the bladder in transplants involving the whole pancreas. *Surg Gynecol Obstet* 1989; **169**: 169-171 [PMID: 2667177]

9 **Gruessner RW**. Recipient procedures. In: Gruessner RW, Sutherland DE. Transplantation of the pancreas. New York: Springer-Verlag Inc, 2004: 150-178 [DOI: 10.1007/978-1-4757-4371-5]

10 **Torigian DA**, Banner MP, Ramchandani P. Imaging urologic complications of pancreas transplantation with bladder drainage. *Clin Imaging* 2000; **24**: 132-138 [PMID: 11150678 DOI: 10.1016/s0899-7071(00)00183-2]

11 **Stratta RJ**, Sindhi R, Sudan D, Jerius JT, Radio SJ. Duodenal segment complications in vascularized pancreas transplantation. *J Gastrointest Surg* 1997; **1**: 534-544 [PMID: 9834389 DOI: 10.1016/s1091-255x(97)80070-4]

12 **Henry ML**, Elkhammas EA, Bumgardner GL, Pelletier RP, Ferguson RM. Outcome of 300 consecutive pancreas-kidney transplants. *Transplant Proc* 1998; **30**: 291 [PMID: 9532045 DOI: 10.1016/S0041-1345(97)01274-8]

13 **Del Pizzo JJ**, Jacobs SC, Bartlett ST, Sklar GN. Urological complications of bladder-drained pancreatic allografts. *Br J Urol* 1998; **81**: 543-547 [PMID: 9598625 DOI: 10.1046/j.1464-410x.1998.00619.x]

14 **Gettman MT**, Levy JB, Engen DE, Nehra A. Urological complications after kidney-pancreas transplantation. *J Urol* 1998; **159**: 38-42; discussion 42 [PMID: 9400432 DOI: 10.1016/s0022-5347(01)64005-9]

15 **Medina Polo J**, Morales JM, Blanco M, Aguirre JF, Andrés A, Díaz R, Jiménez C, Leiva O, Meneu JC, Moreno E, Pamplona M, Passas J, Rodríguez A, de la Rosa F. Urological complications after simultaneous pancreas-kidney transplantation. *Transplant Proc* 2009; **41**: 2457-2459 [PMID: 19715950 DOI: 10.1016/j.transproceed.2009.06.065]

16 **Sudan D**, Sudan R, Stratta R. Long-term outcome of simultaneous kidney-pancreas transplantation:

analysis of 61 patients with more than 5 years follow-up. *Transplantation* 2000; **69**: 550-555 [PMID: 10708110 DOI: 10.1097/00007890-200002270-00015]

17 **Sollinger HW**, Ploeg RJ, Eckhoff DE, Stegall MD, Isaacs R, Pirsch JD, D'Alessandro AM, Knechtle SJ, Kalayoglu M, Belzer FO. Two hundred consecutive simultaneous pancreas-kidney transplants with bladder drainage. *Surgery* 1993; **114**: 736-743; discussion 743 [PMID: 8211688]

18 **Sollinger HW**, Messing EM, Eckhoff DE, Pirsch JD, D'Alessandro AM, Kalayoglu M, Knechtle SJ, Hickey D, Belzer FO. Urological complications in 210 consecutive simultaneous pancreas-kidney transplants with bladder drainage. *Ann Surg* 1993; **218**: 561-8; discussion 568 [PMID: 8215647 DOI: 10.1097/00000658-199310000-00016]

19 **Blanchet P**, Droupy S, Eschwege P, Hammoudi Y, Durrbach A, Charpentier B, Benoit G. Urodynamic testing predicts long-term urological complications following simultaneous pancreas-kidney transplantation. *Clin Transplant* 2003; **17**: 26-31 [PMID: 12588318 DOI: 10.1034/j.1399-0012.2003.02026.x]

20 **Nath DS**, Gruessner A, Kandaswamy R, Gruessner RW, Sutherland DE, Humar A. Late anastomotic leaks in pancreas transplant recipients - clinical characteristics and predisposing factors. *Clin Transplant* 2005; **19**: 220-224 [PMID: 15740558 DOI: 10.1111/j.1399-0012.2005.00322.x]

21 **Troppmann C**. Surgical complications. In: Gruessner RWG, Sutherland DER. Pancreas transplantation. New York: Springer, 2004: 206-237

22 **deGroat WC**, Booth AM. Physiology of the urinary bladder and urethra. *Ann Intern Med* 1980; **92**: 312-315 [PMID: 6243894 DOI: 10.7326/0003-4819-92-2-312]

23 **Stephanian E**, Gruessner RW, Brayman KL, Gores P, Dunn DL, Najarian JS, Sutherland DE. Conversion of exocrine secretions from bladder to enteric drainage in recipients of whole pancreaticoduodenal transplants. *Ann Surg* 1992; **216**: 663-672 [PMID: 1466620 DOI: 10.1097/00000658-199212000-00008]

24 **Fernandez-Cruz L**, Sabater L, Gilabert R, Ricart MJ, Saenz A, Astudillo E. Native and graft pancreatitis following combined pancreas-renal transplantation. *Br J Surg* 1993; **80**: 1429-1432 [PMID: 7504566 DOI: 10.1002/bjs.1800801125]

25 **Wengrovitz M**, Jamwenko MV, Gifford RRM, Sechtin AG, Mandell MJ, Yang HC. Stone formation as a cause of allograft pancreatitis in the recipient of a combined kidney and pancreas transplant. *Clin Transplant* 1990; **4**: 117-119

26 **Hickey DP**, Bakthavatsalam R, Bannon CA, O'Malley K, Corr J, Little DM. Urological complications of pancreatic transplantation. *J Urol* 1997; **157**: 2042-2048 [PMID: 9146576 DOI: 10.1016/S0022-5347(01)64670-6]

27 **Hakim NS**, Gruessner AC, Papalois BE, Troppmann C, Dunn DL, Sutherland DE, Gruessner RW. Duodenal complications in bladder-drained pancreas transplantation. *Surgery* 1997; **121**: 618-624 [PMID: 9186461 DOI: 10.1016/s0039-6060(97)90049-0]

28 **Gruessner RW**, Stephanian E, Dunn DL, Gruessner AC, Najarian JS, Sutherland DE. Cystoenteric conversion after whole pancreaticoduodenal transplantation: indications, risk factors, and outcome. *Transplant Proc* 1993; **25**: 1179-1181 [PMID: 8442079]

29 **Senaratne NV**, Norris JM. Bladder *vs* enteric drainage following pancreatic transplantation: How best to support graft survival? *Int J Surg* 2015; **22**: 149-152 [PMID: 26343973 DOI: 10.1016/j.ijsu.2015.08.072]

30 **Adler JT**, Zaborek N, Redfield RR 3rd, Kaufman DB, Odorico JS, Sollinger HW. Enteric conversion after bladder-drained pancreas transplantation is not associated with worse allograft survival. *Am J Transplant* 2019; **19**: 2543-2549 [PMID: 30838785 DOI: 10.1111/ajt.15341]

31 **Choi JY**, Jung JH, Kwon HW, Shin S, Kim YH, Han DJ. Does Enteric Conversion Affect Graft Survival After Pancreas Transplantation with Bladder Drainage? *Ann Transplant* 2018; **23**: 89-97 [PMID: 29391389 DOI: 10.12659/aot.907192]

32 **Van der Werf WJ**, Odorico JS, D'Alessandro AM, Knechtle SJ, Pirsch JD, Kalayoglu M, Sollinger HW. Enteric conversion of bladder-drained pancreas allografts: experience in 95 patients. *Transplant Proc* 1998; **30**: 441-442 [PMID: 9532119 DOI: 10.1016/S0041-1345(97)01347-X]

33 **Sollinger HW**, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg* 2009; **250**: 618-630 [PMID: 19730242 DOI: 10.1097/SLA.0b013e3181b76d2b]

34 **Sindhi R**, Stratta RJ, Lowell JA, Sudan D, Cushing KA, Castaldo P, Jerius JT. Experience with enteric conversion after pancreatic transplantation with bladder drainage. *J Am Coll Surg* 1997; **184**: 281-289 [PMID: 9060926]

35 **Fernandez-Cruz L**, Ricart MJ, Astudillo E, Sabater L, Fondevila C, Prados M. Enteric drainage as primary procedure and after cystoenteric conversion in whole pancreaticoduodenal transplantation. *Transplant Proc* 1997; **29**: 643-644 [PMID: 9123458 DOI: 10.1016/S0041-1345(96)00376-4]

36 **van de Linde P**, van der Boog PJ, Baranski AG, de Fijter JW, Ringers J, Schaapherder AF. Pancreas transplantation: advantages of both enteric and bladder drainage combined in a two-step approach. *Clin Transplant* 2006; **20**: 253-257 [PMID: 16640535 DOI: 10.1111/j.1399-0012.2005.00477.x]

37 **Kaplan AJ**, Valente JF, First MR, Demmy AM, Munda R. Early operative intervention for urologic complications of kidney-pancreas transplantation. *World J Surg* 1998; **22**: 890-894 [PMID: 9673565 DOI: 10.1007/s002689900488]

38 **Connolly EM**, Baktavatsalam R, O'Malley K, Little DM, Hickey DP. Enteric conversion after bladder-drained pancreatic transplantation; a simple and safe salvage procedure. *Eur J Surg* 2001; **167**: 371-374 [PMID: 11419554 DOI: 10.1080/110241501750215276]

39 **Riad SM**, Keys DO, Jackson S, Vakil V, Berglund D, Matas A, Finger EB, Kandaswamy R. Enteric Conversion of Bladder-drained Pancreas as a Predictor of Outcomes in Almost 600 Recipients at a Single Center. *Transplant Direct* 2020; **6**: e550 [PMID: 32548244 DOI: 10.1097/TXD.0000000000000997]

40 **Akateh C**, Rajab A, Henry M, El-Hinnawi A. Enterovesical Fistula After Enteric Conversion of a Bladder-Drained Pancreatic Allograft: A Case Report. *Exp Clin Transplant* 2019; **17**: 274-277 [PMID: 28540837 DOI: 10.6002/ect.2016.0237]

41 **Sutherland DE**, Gruessner RW, Dunn DL, Matas AJ, Humar A, Kandaswamy R, Mauer SM, Kennedy WR, Goetz FC, Robertson RP, Gruessner AC, Najarian JS. Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann Surg* 2001; **233**: 463-501 [PMID: 11303130 DOI: 10.1097/00000658-200104000-00003]

42 **Sugitani A**, Gritsch HA, Shapiro R, Bonham CA, Egidi MF, Corry RJ. Surgical complications in 123 consecutive pancreas transplant recipients: comparison of bladder and enteric drainage. *Transplant Proc* 1998; **30**: 293-294 [PMID: 9532047 DOI: 10.1016/s0041-1345(97)01276-1]

43 **Corry RJ**, Chakrabarti P, Shapiro R, Jordan ML, Scantlebury VP, Vivas CA. Comparison of enteric *vs* bladder drainage in pancreas transplantation. *Transplant Proc* 2001; **33**: 1647-1651 [PMID: 11267454 DOI: 10.1016/S0041-1345(00)02626-9]

44 **Siskind EJ**, Amodu LI, Pinto S, Akerman M, Jonsson J, Molmenti EP, Ortiz J. Bladder Versus Enteric Drainage of Exocrine Secretions in Pancreas Transplantation: A Retrospective Analysis of the United Network for Organ Sharing Database. *Pancreas* 2018; **47**: 625-630 [PMID: 29683972 DOI: 10.1097/MPA.0000000000001043]

45 **Boggi U**, Amorese G, Marchetti P. Surgical techniques for pancreas transplantation. *Curr Opin Organ Transplant* 2010; **15**: 102-111 [PMID: 20010103 DOI: 10.1097/MOT.0b013e32833553de]

46 **Rogers J**, Farney AC, Orlando G, Farooq U, Al-Shraideh Y, Stratta RJ. Pancreas transplantation with portal venous drainage with an emphasis on technical aspects. *Clin Transplant* 2014; **28**: 16-26 [PMID: 24410731 DOI: 10.1111/ctr.12275]

47 **Fridell JA**, Milgrom ML, Henson S, Pescovitz MD. Use of the end-to-end anastomotic circular stapler for creation of the duodenoenterostomy for enteric drainage of the pancreas allograft [corrected]. *J Am Coll Surg* 2004; **198**: 495-497 [PMID: 15008165 DOI: 10.1016/j.jamcollsurg.2003.09.006]

48 **Lam VW**, Wong K, Hawthorne W, Ryan B, Lau H, Robertson P, Allen RD, Pleass H. The linear cutting stapler for enteric anastomosis: a new technique in pancreas transplantation. *Transpl Int* 2006; **19**: 915-918 [PMID: 17018127 DOI: 10.1111/j.1432-2277.2006.00368.x]

49 **Ferrer J**, Molina V, Rull R, López-Boado MÁ, Sánchez S, García R, Ricart MJ, Ventura-Aguiar P, García-Criado Á, Esmatjes E, Fuster J, Garcia-Valdecasas JC. Pancreas transplantation: Advantages of a retroperitoneal graft position. *Cir Esp* 2017; **95**: 513-520 [PMID: 28688516 DOI: 10.1016/j.ciresp.2017.05.004]

50 **Lindahl JP**, Horneland R, Nordheim E, Hartmann A, Aandahl EM, Grzyb K, Haugaa H, Kjøsen G, Åsberg A, Jenssen T. Outcomes in Pancreas Transplantation With Exocrine Drainage Through a Duodenoduodenostomy Versus Duodenojejunostomy. *Am J Transplant* 2018; **18**: 154-162 [PMID: 28696022 DOI: 10.1111/ajt.14420]

51 **Linhares MM**, Beron RI, Gonzalez AM, Tarazona C, Salzedas A, Rangel EB, Sá JR, Melaragno C, Goldman SM, Souza MG, Sato NY, Matos D, Lopes-Filho GJ, Medina JO. Duodenum-stomach anastomosis: a new technique for exocrine drainage in pancreas transplantation. *J Gastrointest Surg* 2012; **16**: 1072-1075 [PMID: 22258867 DOI: 10.1007/s11605-011-1806-1]

52 **Moya-Herraiz A**, Muñoz-Bellvis L, Ferrer-Fábrega J, Manrique Municio A, Pérez-Daga JA, Muñoz-Casares C, Alarcó-Hernández A, Gómez-Gutiérrez M, Casanova-Rituerto D, Sanchez-Bueno F, Jimenez-Romero C, Fernández-Cruz Pérez L. Cooperative Study of the Spanish Pancreas Transplant Group (GETP): Surgical Complications. *Cir Esp* 2015; **93**: 300-306 [PMID: 25638511 DOI: 10.1016/j.ciresp.2014.12.006]

53 **Goodman J**, Becker YT. Pancreas surgical complications. *Curr Opin Organ Transplant* 2009; **14**: 85-89 [PMID: 19337152 DOI: 10.1097/MOT.0b013e328320a8ec]

54 **Lall CG**, Sandrasegaran K, Maglinte DT, Fridell JA. Bowel complications seen on CT after pancreas transplantation with enteric drainage. *AJR Am J Roentgenol* 2006; **187**: 1288-1295 [PMID: 17056918 DOI: 10.2214/AJR.05.1087]

55 **Orsenigo E**, Cristallo M, Socci C, Castoldi R, Fiorina P, Invernizzi L, Caldara R, Secchi A, Di Carlo V. Successful surgical salvage of pancreas allograft. *Transplantation* 2003; **75**: 233-236 [PMID: 12548130 DOI: 10.1097/01.TP.0000041784.27763.A9]

56 **Uva PD**, Villavicencio Fornaciari S, Giunippero AE, Cabrera IC, Casadei DH. Case report: pancreas graft with a duodenal complication rescued using total duodenectomy. *Transplant Proc* 2014; **46**: 3068-3071 [PMID: 25420824 DOI: 10.1016/j.transproceed.2014.07.019]

57 **Boggi U**, Vistoli F, Del Chiaro M, Moretto C, Croce C, Signori S, D'Imporzano S, Amorese G, Campani D, Calabrese F, Capocasale E, Marchetti P. Total duodenectomy with enteric duct drainage: a rescue operation for duodenal complications occurring after pancreas transplantation. *Am J Transplant* 2010; **10**: 692-697 [PMID: 20121744 DOI: 10.1111/j.1600-6143.2009.02981.x]

58 **Reddy MS**, White SA, Jaques BC, Torpey N, Manas DM. Pancreas graft salvage using pancreatico-duodenectomy with enteric drainage. *Am J Transplant* 2007; **7**: 2422-2424 [PMID: 17845576 DOI: 10.1111/j.1600-6143.2007.01931.x]

59 **Al-Adra D**, McGilvray I, Goldaracena N, Spetzler V, Laurence J, Norgate A, Marquez M, Greig P,

Sapisochin G, Schiff J, Singh S, Selzner M, Cattral M. Preserving the Pancreas Graft: Outcomes of Surgical Repair of Duodenal Leaks in Enterically Drained Pancreas Allografts. *Transplant Direct* 2017; **3**: e179 [PMID: 28706982 DOI: 10.1097/TXD.0000000000000698]

60 **Hesse UJ**, Meester D, Troisi R, Cathenis K, Lameire N, Hemptinne B. The use of low dose octreotide prophylaxis in pancreatic transplants with enteric drainage. Results of a prospective randomized single center trial. Clin Transplant 2005; 19: 299-303 [PMID: 15877788 DOI: 10.1111/j.1399-0012.2005.00208.x]

61 **Benedetti E**, Coady NT, Asolati M, Dunn T, Stormoen BM, Bartholomew AM, Vasquez EM, Pollak R. A prospective randomized clinical trial of perioperative treatment with octreotide in pancreas transplantation. *Am J Surg* 1998; **175**: 14-17 [PMID: 9445231 DOI: 10.1016/s0002-9610(97)00236-5]

62 **Boggi U**, Vistoli F, Signori S, Del Chiaro M, Campatelli A, Amorese G, Marciano E, Coppelli A, Tregnaghi C, Rizzo G, Marchetti P, Mosca F. A technique for retroperitoneal pancreas transplantation with portal-enteric drainage. *Transplantation* 2005; **79**: 1137-1142 [PMID: 15880057 DOI: 10.1097/01.tp.0000157279.39761.cc]

63 **Kahn J**, Iberer F, Kniepeiss D, Duller D, Jakoby E, Tscheliessnigg K. Retroperitoneal pancreas transplantation with systemic-enteric drainage--case report. *Clin Transplant* 2008; **22**: 674-676 [PMID: 18435782 DOI: 10.1111/j.1399-0012.2008.00830.x]

64 **Ono S**, Kuroki T, Kitazato A, Adachi T, Chen YY, Chen SC, Eguchi S, Shyr YM, Wang SE. Simultaneous pancreas and kidney composite graft transplantation with retroperitoneal systemic-enteric drainage. *Ann Transplant* 2014; **19**: 586-590 [PMID: 25389032 DOI: 10.12659/AOT.891350]

65 **Walter M**, Jazra M, Kykalos S, Kuehn P, Michalski S, Klein T, Wunsch A, Viebahn R, Schenker P. 125 Cases of duodenoduodenostomy in pancreas transplantation: a single-centre experience of an alternative enteric drainage. *Transpl Int* 2014; **27**: 805-815 [PMID: 24750305 DOI: 10.1111/tri.12337]

66 **Herrero-Martínez JM**, Lumbreras C, Manrique A, San-Juan R, García-Reyne A, López-Medrano F, Lizasoain M, de Dios B, Andrés A, Jiménez C, Gutiérrez E, Moreno E, Aguado JM. Epidemiology, risk factors and impact on long-term pancreatic function of infection following pancreas-kidney transplantation. *Clin Microbiol Infect* 2013; **19**: 1132-1139 [PMID: 23480521 DOI: 10.1111/1469-0691.12165]

67 **Rostambeigi N**, Kudva YC, John S, Mailankody S, Pedersen RA, Dean PG, Prieto M, Cosio FG, Kremers WK, Walker RC, Abraham RS, Stegall MD. Epidemiology of infections requiring hospitalization during long-term follow-up of pancreas transplantation. *Transplantation* 2010; **89**: 1126-1133 [PMID: 20164817 DOI: 10.1097/TP.0b013e3181d54bb9]

68 **Michalak G**, Kwiatkowski A, Czerwinski J, Chmura A, Wszola M, Nosek R, Ostrowski K, Danielewicz R, Lisik W, Adadynski L, Małkowski P, Fesolowicz S, Bieniasz M, Kasprzyk T, Durlik M, Walaszewski J, Rowinski W. Surgical complications of simultaneous pancreas-kidney transplantation: a 16-year-experience at one center. *Transplant Proc* 2005; **37**: 3555-3557 [PMID: 16298659 DOI: 10.1016/j.transproceed.2005.09.077]

69 **Bodro M**, Ferrer J, Ricart MJ, Sanclemente G, Linares L, Cervera C, Cofan F, Ventura-Aguiar P, Lopez-Boado MÁ, Marco F, Fuster J, García-Valdecasas JC, Moreno A. Epidemiology, risk factors, and impact of bacterial infections on outcomes for pancreatic grafts. *Clin Transplant* 2018; **32**: e13333 [PMID: 29920780 DOI: 10.1111/ctr.13333]

70 **Troppmann C**. Complications after pancreas transplantation. *Curr Opin Organ Transplant* 2010; **15**: 112-118 [PMID: 20009931 DOI: 10.1097/MOT.0b013e3283355349]

71 **Troppmann C**, Pierce JL, Gandhi MM, Gallay BJ, McVicar JP, Perez RV. Higher surgical wound complication rates with sirolimus immunosuppression after kidney transplantation: a matched-pair pilot study. *Transplantation* 2003; **76**: 426-429 [PMID: 12883205 DOI: 10.1097/01.TP.0000072016.13090.4E]

72 **Humar A**, Kandaswamy R, Drangstveit MB, Parr E, Gruessner AG, Sutherland DE. Prolonged preservation increases surgical complications after pancreas transplants. *Surgery* 2000; **127**: 545-551 [PMID: 10819063 DOI: 10.1067/msy.2000.104742]

73 **Kotton CN**, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, Humar A; Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013; **96**: 333-360 [PMID: 23896556 DOI: 10.1097/TP.0b013e31829df29d]

74 **Biancofiore G**, Bindi ML, Romanelli AM, Boldrini A, Consani G, Bisà M, Filipponi F, Vagelli A, Mosca F. Intra-abdominal pressure monitoring in liver transplant recipients: a prospective study. *Intensive Care Med* 2003; **29**: 30-36 [PMID: 12528019 DOI: 10.1007/s00134-002-1552-7]

75 **Kathemann S**, Dohna-Schwake C, Paul A, Hoyer PF, Gerner P. Intraabdominal Pressure Monitoring in Pediatric Liver Transplant Recipients: A Useful Tool for the Detection of Abdominal Compartment Syndrome. *Transplantation* 2012; **94**: 665 [DOI: 10.1097/00007890-201211271-01301]

76 **Bressan AK**, Kirkpatrick AW, Ball CG. Abdominal intra-compartment syndrome - a non-hydraulic model of abdominal compartment syndrome due to post-hepatectomy hemorrhage in a man with a localized frozen abdomen due to extensive adhesions: a case report. *J Med Case Rep* 2016; **10**: 251 [PMID: 27633658 DOI: 10.1186/s13256-016-1045-x]

77 **Bressan AK**, Ball CG. Intra-abdominal hypertension and abdominal compartment syndrome in acute pancreatitis, hepato-pancreato-biliary operations and liver transplantation. *Anaesthesiol Intensive Ther* 2017; **49**: 159-166 [PMID: 28513820 DOI: 10.5603/AIT.a2017.0024]

78 **Kirkpatrick AW**, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J,

Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C; Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013; **39**: 1190-1206 [PMID: 23673399 DOI: 10.1007/s00134-013-2906-z]

79 **Basu A**. Elevated intra-abdominal pressure is a "second-hit". *World J Surg* 2010; **34**: 1144; author reply 1145 [PMID: 20066415 DOI: 10.1007/s00268-009-0384-9]

80 **Malbrain ML**, Peeters Y, Wise R. The neglected role of abdominal compliance in organ-organ interactions. *Crit Care* 2016; **20**: 67 [PMID: 26983963 DOI: 10.1186/s13054-016-1220-x]

81 **Hobeika C**, Allard MA, Bucur PO, Naili S, Sa Cunha A, Cherqui D, Castaing D, Adam R, Vibert E. Management of the Open Abdomen after Liver Transplantation. *World J Surg* 2017; **41**: 3199-3204 [PMID: 28717912 DOI: 10.1007/s00268-017-4125-1]

82 **Boggi U**, Signori S, Vistoli F, D'Imporzano S, Amorese G, Consani G, Guarracino F, Marchetti P, Focosi D, Mosca F. Laparoscopic robot-assisted pancreas transplantation: first world experience. *Transplantation* 2012; **93**: 201-206 [PMID: 22245834 DOI: 10.1097/TP.0b013e318238daec]

83 **Tzvetanov I**, D'Amico G, Bejarano-Pineda L, Benedetti E. Robotic-assisted pancreas transplantation: where are we today? *Curr Opin Organ Transplant* 2014; **19**: 80-82 [PMID: 24346147 DOI: 10.1097/MOT.0000000000000044]

84 **Yeh CC**, Spaggiari M, Tzvetanov I, Oberholzer J. Robotic pancreas transplantation in a type 1 diabetic patient with morbid obesity: A case report. *Medicine (Baltimore)* 2017; **96**: e5847 [PMID: 28178127 DOI: 10.1097/MD.0000000000005847]

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MINIREVIEWS

Late complications of pancreas transplant

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Abstract

To summarize the long-term complications after pancreas transplantation that affect graft function, a literature search was carried out on the long-term complications of pancreatic transplantation, namely, complications from postoperative 3rd mo onwards, in terms of loss of graft function, late infection and vascular complications as pseudoaneurysms. The most relevant reviews and studies were selected to obtain the current evidence on these topics. The definition of graft failure varies among different studies, so it is difficult to evaluate, a standardized definition is of utmost importance to know the magnitude of the problem in all worldwide series. Chronic rejection is the main cause of long-term graft failure, occurring in 10% of patients. From the 3rd mo of transplantation onwards, the main risk factor for late infections is immunosuppression, and patients have opportunistic infections like: Cytomegalovirus, hepatitis B and C viruses, Epstein-Barr virus and varicella-zoster virus; opportunistic bacteria, reactivation of latent infections as tuberculosis or fungal infections. Complete preoperative studies and serological tests should be made in all recipients to avoid these infections, adding perioperative prophylactic treatments when indicated. Pseudoaneurysm are uncommon, but one of the main causes of late bleeding, which can be fatal. The treatment should be performed with radiological endovascular approaches or open surgery in case of failure. Despite all therapeutic options for the complications mentioned above, transplantectomy is a necessary option in approximately 50% of relaparotomies, especially in life-threatening complications. Late complications in pancreatic transplantation threatens long-term graft function. An exhaustive follow-up as well as a correct immunosuppression protocol are necessary for prevention.

Key Words: Pancreas transplantation; Pancreas allograft failure; Pancreas transplant rejection; Pseudoaneurysm; Allograft pancreatectomy

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Core Tip: Late complications after pancreas transplant (> 3 mo after surgery) may occur, endangering loss of graft function. Chronic rejection is the main cause of long-term graft failure, occurring in 10% of patients, so targeted immunosuppressive therapy is important to prevent it; however, it predisposes to opportunistic viral, bacterial and fungal infections, and even the reactivation of latent infections, which should be prevented with perioperative prophylaxis and treated when necessary. Pseudoaneurysm should be early diagnosed, and treated by endovascular approach when possible, to prevent bleeding. Nonetheless, in some late complications, transplantectomy is a necessary option, especially in life-threatening complications.

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INTRODUCTION

Pancreas transplantation is currently the most effective method to establish durable normoglycemia for patients with diabetes mellitus[1], and therefore achieves the benefits demonstrated with intensive insulin therapy, but without hypoglycemic complications derived from that treatment. Pancreatic graft loss may occur due to several complications, such as technical failure in the early postoperative period, but also late complications (which occur from postoperative 3rd mo onwards), among which the most relevant are chronic rejection, late infections and vascular complications as pseudoaneurysms. In recent years, pancreatic graft long-term survival has improved, with a half-life longer than 14 years in simultaneous pancreas and kidney (SPK) transplantation, which is the most frequent modality of pancreas transplantation as it is associated with better allograft survival[2]. In this review, we will describe the late complications of pancreas transplant and recent trends in their prevention, diagnosis and treatment.

LOSS OF GRAFT FUNCTION

The Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) Pancreas Transplantation Committee approved precise definitions of pancreas graft failure in early 2018. Some of the definitions are concrete, such as a recipient's transplanted pancreas is removed, a recipient re-registers for pancreas transplant, a recipient registers for an islet transplant after undergoing pancreas transplant, or a recipient dies. Pancreas graft failure can also be defined if a recipient's total insulin use is greater than or equal to 0.5 units/kg/d for a consecutive 90 d. The latter definition may be problematic if the recipient's starting insulin dose is less than 0.5 units/kg/d[2].

Recently the consensus report from the International Pancreas & Islet Transplant Association and European Pancreas & Islet Transplantation Association[3] defined the outcomes of beta–cell (b-cell) replacement therapy: Optimal b-cell graft function is defined by near-normal glycemic control (HbA1c ≤ 6.5% [48 mmol/mol]) without severe hypoglycemia or requirement for insulin or other antihyperglycemic therapy, and with an increase over pretransplant measurement of C-peptide. Good b-cell graft function requires HbA1c < 7.0% (53 mmol/mol) without severe hypoglycemia and with a significant (> 50%) reduction in insulin requirements and restoration of clinically significant C-peptide production. Marginal b-cell graft function is defined by failure to achieve HbA1c < 7.0% (53 mmol/mol), the occurrence of any severe hypoglycemia, or less than 50% reduction in insulin requirements when there is restoration of clinically significant C-peptide production documented by improvement in hypoglycemia awareness/severity, or glycemic variability/lability. A failed b-cell graft is defined by the absence of any evidence for clinically significant C-peptide production. Optimal and good functional outcomes are considered successful clinical outcomes.

Although these newer definitions have not yet been reflected, reported early overall rate of pancreas graft failure (within the first 90 d) in 2018 was 5.9%, and 5-year pancreas graft survival rates were 73% for SPK, 65% for pancreas after kidney (PAK), and 53% for pancreas transplant alone (PTA)[2]. These results are similar in Spain, with a 5-year graft survival rate of 72%-74% for SPK[4].

Adverse technical and immunological events within the 1st year need to be avoided under all circumstances; what happens in the 1st year posttransplant has a very strong impact on long-term graft function[5]. The main cause of pancreas graft loss within the first 3 mo usually is technical failure: Graft thrombosis (10%-35%) followed by intraabdominal infections and pancreatitis[6]. An adequate immunosuppression therapy with tight control is recommended to avoid pancreas allograft rejection, since it is also one of the main causes of graft failure. Acute rejection usually develops 1 wk to 3 mo after transplantation but can occur earlier or later, it is difficult to diagnose, but may be suspected when loss of allograft function (hyperglycemia) is associated with high level of serum amylase and/or lipase. Early detection is essential to institute antirejection treatment and avert graft failure. Incidence in OPTN/UNOS data of a first rejection episode is improving over time, with low rates respect previous data for all categories of pancreas transplant, in 2016-2017 in the United States it was: 11.7%, 19.2%, and 12.4% following PAK, PTA and SPK respectively[2]. In the same way, global incidence of rejection in Spain series was 10.9% in SPK during last decade[4]. These low rejection rates clearly reflect ongoing improvements in immunosuppression protocols. In fact, the avoidance of acute rejection episodes is probably the single highest impact on excellent long-term function[5].

There is some controversy regarding immunosuppressive treatment in pancreas transplantation. Standard protocols include use of induction therapy followed by maintenance immunosuppression, but the amount, frequency and duration of each therapy, especially the induction treatment has not been clearly defined, which consist in T-cell depleting agent (*e.g.*, antithymocyte globulin and alemtuzumab), even though it has been adopted by most centers (> 80%). Maintenance immunosuppressive therapy for pancreatic transplantation is similar for that used for kidney transplantation. A combination of a calcineurin inhibitor (predominantly tacrolimus), an antimetabolite (mycophenolate mofetil or mycophenolate sodium), is associated to low-dose corticosteroids therapy in approximately 60% of the centers[2]. However, taking into account the metabolic side effects as well as the increased risk of infection associated with the use of steroids[7], some studies have suggested early steroid withdrawal or steroid free regimens in these patients, particularly after the introduction of induction therapy with T-cell depleting agents, but there is currently insufficient evidence for the benefits and harms of this therapy[8]. There is also a trend to incorporate mammalian target of rapamycin (mTOR) inhibitors over mycophenolate in combination with tacrolimus into immunosuppressive protocol, because rapamycin appears to be more effective in preventing acute rejection, but it must be weighed against its potential negative metabolic consequences and the accentuation of the nephrotoxicity of the calcineurin inhibitor and wound-healing complications[9-11], so at the moment it has not been widely adopted. Future research should focus on developing personalized immune assessment of transplant patients, through non-invasive tests of immunological biomarkers to monitor the recipient's immune status[12]. These tests will permit recipient-specific tailored immunosuppressive protocols, based on their immunity response and individual risk, minimizing the complications of excessive immunosuppression while maintaining a low incidence of rejection.

Chronic rejection remains the main cause of long-term graft failure after 1 year, occurring in 10% of patients[13,14]. It may be the result of recurrent episodes of acute rejection with posterior fibrosis, atrophy, and eventual loss of graft function. Therefore, effective immunosuppression protocols and close monitoring of pancreas and kidney allograft function are the best way to prevent it. The image tests findings of acute and chronic rejections are relatively nonspecific and unreliable, making it difficult to diagnose[15]. Diagnostic confirmation must be performed by needle core pancreas allograft biopsy, preferably percutaneous ultrasound-guided biopsy[16]. The Banff schema for grading pancreas allograft rejection based on pathological findings, differentiate the type (T-cell-mediated rejection or antibody-mediated pancreas allograft rejection) and the grade (mild, moderate, and severe) with a high diagnostic accuracy, helping to select the appropriate treatment in each case[17,18].

Given the possibility of chronic rejection, type 1 diabetes mellitus recurrence should also be suspected, which is an infrequent entity, appearing approximately in 3%-7% of properly immunosuppressed patients[19]. It occurs due to the presence of antibodies against pancreatic beta cells in the recipient (type 1 diabetes-associated autoantibodies

to the autoantigens GAD65, IA-2, and ZnT8) causing destruction of the pancreatic islets (insulitis). Usually the antibody conversion precede hyperglycemia by a variable length of time, and negative autoimmunity prior to transplantation does not ensure that autoimmune diabetes will not recur. Unlike rejection, serum amylase and lipase levels usually do not rise, and there is no effective treatment, as the increase in immunosuppression does not improve the progression of islet autoimmunity. Diagnostic confirmation must be performed by percutaneous biopsy, in which a variable degree of insulitis and loss of insulin staining must be seen, sometimes associated to minimal to moderate and rarely severe pancreas and/or kidney transplant rejection[20].

The 5-year mortality for SPK in OPTN/UNOS data[2] and Spanish series[4] ranges over 7% to 8%. Long-term mortality data reflect the high cardiovascular comorbidity in this population, with 10-year mortality 26.8%, 20.1%, and 25.3% for PAK, PTA, and SPK, respectively. Despite effective glycemia control after pancreas transplantation delays progression of microvascular complications and improves survival in diabetic patients, cardiovascular comorbidity is the main factor that threatens long-term survival of pancreas transplant patients[5], so its optimal control is another of the priority objectives in the follow up of this patients.

There has been controversy regarding transplant center volume and the risk of short and long-term pancreas graft failure, so it has been analyzed by several studies, highlighting that patient and graft survival after pancreas transplantation are superior in higher volume centers (> 13 transplants/year) than in lower volume centers[21,22], or at least equal even though they transplant organs with the highest pancreas donor risk index[23]. The explanation for inferior outcomes in low-volume centers is likely to be complex, but center volume could be a surrogate marker for adequate recipient selection, surgical expertise, multidisciplinary preoperative, and postoperative inpatient and outpatient care, and appropriate long-term follow-up. Actually, approximately two-thirds of pancreas transplants are performed at programs that perform more than 10 transplants per year, and these numbers have not changed substantially over the past decade[2], this may have contributed to explain the improvement of global pancreas allograft and patient survival throughout last years, demonstrating a better management in these demanding patients over time.

CHRONIC INFECTION

Approximately 63% of pancreas transplant recipients develop a serious infection during the first 5 years of follow-up[24]. Many of the infections in pancreas transplantation follow a typical temporal pattern. Three periods have been described based on the predominance of certain infections: In the first period (1st mo), bacterial infections derived from the surgical procedure are typical. In the second period (2-6 mo), the main risk factor is immunosuppression, and patients basically have de novo opportunistic infections or reactivation of latent diseases: Cytomegalovirus (CMV), herpes simplex virus type 6 (VHV), hepatitis B and C viruses (HBV/HCV), Epstein-Barr virus (EBV) and varicella-zoster virus (VZV); and opportunistic bacteria: *Pneumocystis jiroveci* pneumonia, *Nocardia, Listeria monocytogenes*, *Toxoplasma gondii*, and fungal infections, among others. During the third period (after the 6th mo), in patients with good allograft function, the majority of infections are those acquired in the community, similar to the general population, although opportunistic infections may also occur, by reactivation of certain latent viruses (BK virus, CMV…)[7]. In addition, tumors related to viral infections such as vulgar warts and post-transplant lymphoproliferative diseases, especially due to EBV, may develop in this period[25].

Prevention of infections

Prophylaxis before transplant: Prevention of infection begins with the adequate selection of the donor and a rigorous evaluation of the recipient with an exhaustive physical examination and study of viral serological markers: CMV, EBV, VZV, HBV, HCV, HIV toxoplasmosis, *Treponema pallidum* serology, and some others that can vary according to the epidemiology of each geographic area. This permits us to diagnose and treat active infections in the candidates, make decisions about their acceptance or exclusion, and identify the risk factors. Moreover, vaccinations must be completed before the transplantation according to the protocol of each center and geographical area[24].

Perioperative prophylaxis: At the time of the transplant surgery, prophylactic

administration of antibiotics like cephalosporins, or ampicillin-sulbactam as an alternative, every 2 h during surgery, and maintenance until 48 h after surgery is recommended. Antifungals (fluconazole) are also associated in a single dose during surgery, and in postoperative prophylaxis regimen up to 14 d in cases of increased risk of infection[26]. The choice of therapeutic agent, both for prophylaxis and for empirical treatment, will also depend on the incidence and type of microorganisms isolated in each center.

The use of cotrimoxazole at low doses until the 6th mo post-transplant has decreased the incidence of *Pneumocystis pneumonia*[27]. Likewise, it constitutes an excellent prophylaxis to avoid infection by intracellular bacteria, such as *Listeria monocytogenes* and *Nocardia spp.*

CMV prophylaxis and monitoring after transplantation: CMV infections are one of the most frequent complications affecting solid organ transplant recipients, conveying higher risk of graft loss, morbidity and mortality. Given that the CMV serostatus of donor and recipient (D/R) are key predictors of the risk of CMV after transplant, and guide decisions on antiviral prophylaxis or preemptive treatment. A measurement of CMV-specific IgG should be performed, and if the donor or recipient is seronegative during the pretransplant evaluation, serology should be repeated at the time of the transplantation. According to the guidelines of the latest international consensus of 2018 on the management of CMV in solid organ transplants[28], in pancreas transplantation, prophylactic treatment with valganciclovir is recommended based on the risk of CMV infection (Table 1). Other valid option is the preemptive therapy, which consists in the monitoring of CMV viral load in blood at regular intervals (weekly) to detect early viral replication. Once a predetermined assay threshold is achieved (optimally prior to the development of symptoms), antiviral treatment is begun, which should prevent progression to clinical disease. Moreover, there are specific situations that increase the risk of CMV infection, such as in cases where antilymphocyte antibodies for induction are administered, plasmapheresis or HIV infection patients. In these cases, it is also mandatory to administer a prophylactic treatment with valganciclovir, and duration will depend on the degree of immunosuppression of the patient. However, there are resistances associated with currently available therapeutics, as there are series with pancreas-kidney transplant high risk patients (D+/R-) who developed CMV infection/disease despite correct CMV prophylaxis in up to 44%[29]. Novel antivirals therapies are emerging including letermovir, maribavir, and brincidofovir at various states of research development. Future research are needed to evaluate combination therapies for prophylaxis and treatment as well as adjunctive therapies[30].

Furthermore, there is moderate to high-quality evidence of a lower risk of CMV infection in transplant recipients with mTOR inhibitor-based immunosuppressive therapy compared with calcineurin inhibitor-based regimens, therefore a combination of a mTOR inhibitor and a reduced dose of calcineurin inhibitor could be a good alternative in high risk CMV infection patients[31,32].

Prevention of tuberculosis infection: In the pre-transplant evaluation, the possibility of latent tuberculosis infection should be assessed by performing the tuberculin skin test (TST), and/or tests based on the secretion of interferon gamma by memory T cells in response to mycobacterial antigens (interferon gamma release assays) as QuantiFERON TM-TB Gold test. If the result is positive in any of these tests, a prophylactic treatment with isoniazid should be administered, and active tuberculosis infection should also be ruled out. If tuberculosis infection is confirmed, the transplant would be contraindicated until the infection is cured.

According to the guidelines of the European Society for Clinical Microbiology and Infectious Diseases[33], if the TST or QuantiFERON are positive, or the chest X-ray shows lesions of previous tuberculosis, and there is no evidence that the patient have received a correct treatment, chemoprophylaxis with isoniazid for 9 mo should be administered.

PSEUDOANEURYSM

Pseudoaneurysms (PA) occur due to a laceration or disruption of the arterial wall caused by chemical damage due to the exposure to enzymes in the event of pancreatic fistulas or infections with peripancreatic collections, chronic rejections, surgical trauma or biopsies, causing a bleeding into an external fibrous compartment that will contain

Table 1 Recommended approaches for cytomegalovirus prevention for adult pancreas transplant

Serostatus	Risk level	Recommended	Alternate
D-/R-	Low	Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections	Preemptive therapy (if higher risk, *i.e.* significant transfusions)
D+/R-	High	3-6 mo of VGCV	Preemptive therapy
R+	Intermediate	3 mo of VGCV or preemptive therapy	

When a range is given, the duration of prophylaxis may depend on degree of immunosuppression, including the use of antilymphocyte antibodies for induction[28]. VGC: Valganclycovir.

the hematoma. Vascular anastomoses are the most frequent areas affected by PA, but those caused by biopsies usually occur in the pancreatic parenchyma, and can lead to arteriovenous fistulas.

Although PA are infrequent entities, they are one of the main causes of late bleeding, sometimes years after transplantation, which can be lethal. PA tend to debut first with mild digestive hemorrhages, called sentinel bleeding, which can progress to an arteriovenous or arterioenteric fistula[34], preceding of fatal hemorrhage. PA are difficult to detect before the development of massive hemorrhage due to the absence or mildness of the previous symptoms. For this reason, graft control with doppler ultrasonography in the follow up should be performed[35]. Once PA is suspected or demonstrated at ultrasonography, the full anatomy of the PA is best displayed with volumetric high-spatial-resolution CT scanning (angio-CT) or magnetic resonance angiography[14]. Such imaging display is required before planning the treatment (Figure 1).

Current treatment of PA firstly should be performed with radiological endovascular approaches, when possible. Although there is still a lack of reliable data due to the relatively little experience of this approach in pancreas transplant complications, endovascular procedures are becoming more frequently used as they are safe and feasible, but technically demanding. One of the main risks of this approach is the renal function damage caused by contrast agent, but the risk of kidney graft function deterioration, as well as of bleeding due to the high dose of heparin used, seems to be lower than with open surgery[36].

When a PA is diagnosed, elective treatment should be performed to prevent the potential life- and graft-threatening bleeding. The choice between minimally invasive and open surgical repair should be individualized depending on the site of the lesion, the patient status and the multidisciplinary team experience[37,38]. Nevertheless, at the time of acute bleeding, immediate treatment is essential: Endovascular approach with a covered stenting of the involved artery to exclude the PA may provide immediate vascular control in these situations. But if an arteriovenous fistula exists, embolization with microparticles is the treatment of choice[39]. These procedures can be either a definitive treatment[40] or a bridge therapy to posterior open repair[41,42], since rebleeding or necrosis and posterior loss of graft function are not uncommon. For this reason, on many occasions (especially in infections) allograft transplantectomy including the graft vascular anastomosis is performed, requiring sometimes an extra anatomic bypass to maintain blood flow of the lower limb[43].

ALLOGRAFT PANCREATECTOMY: INDICATIONS AND SURGICAL TECHNIQUE

Indications

Surgical complications after pancreas transplantation and later relaparotomies are frequent (25%-30%) and the main cause are thrombosis, bleeding, infection, pancreatitis and bowel obstruction. Unfortunately, it implies allograft pancreatectomy in 50% of cases, and occasionally patient death[44]. The management of such complications has evolved from a low threshold to remove the graft, to considering options for graft preservation through the new antimicrobial and immunosuppressive therapies, as well as the imaging techniques that permit an early diagnosis and image-guided invasive procedures. However, the need to perform a transplantectomy is a necessary situation in some occasions, especially in life-threatening complications. Currently there are no guidelines or consensus that clearly indicate to the surgeon

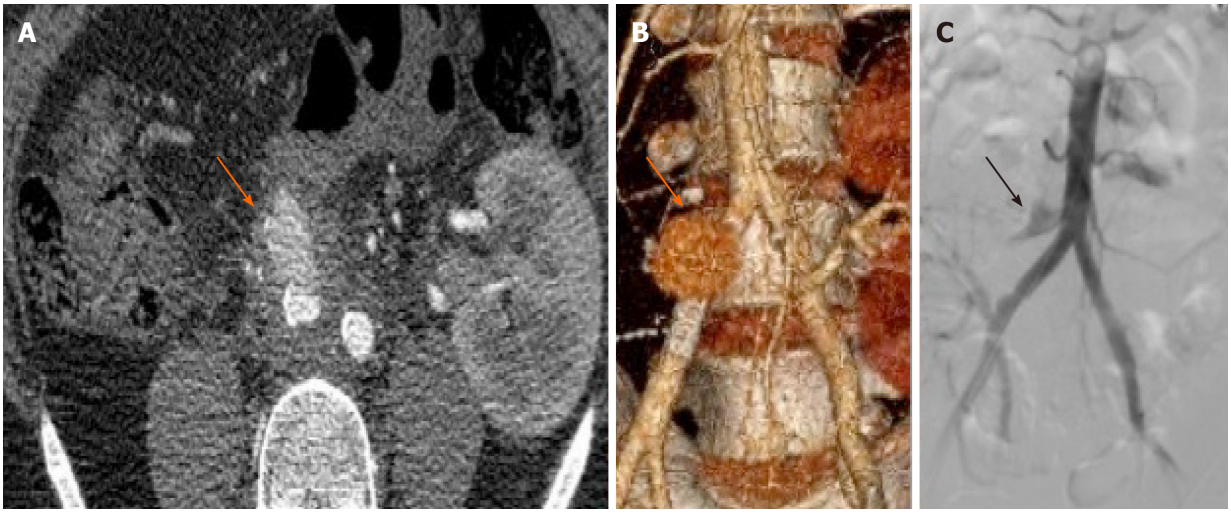

Figure 1 Pseudoaneurysm in the right iliac artery anastomosis of the pancreas graft in a simultaneous pancreas and kidney patient (arrows). A: Angio-computed tomography; B: Three-dimensional reconstruction of iliac artery and pseudoaneurysm; C: Angiography, arterial contrast filling the cavity of the pseudoaneurysm.

when and how it should be performed, but as a general rule, safety of the recipient should be considered as the main factor to take into account.

Thrombosis-related graft necrosis, severe pancreatitis, and uncontrolled duodenal leak constitute the main indications for allograft pancreatectomy during the first 4 wk after transplantation[44]. And late allograft pancreatectomy is usually reserved for recipients with failed grafts, predominantly from chronic rejection who have abdominal and flank pain, gastrointestinal symptoms and/or fever[45]. The rate of allograft pancreatectomy for late graft failure ranges from 25% to 50%, and in these cases the symptoms associated with the failed pancreas graft, risk of formation of arterioenteric fistula, and candidacy for potential retransplantation need to be cautiously evaluated in order to appropriately select the timing and the surgical approach for allograft pancreatectomy[46]. Recent studies show a marked fall in morbidity and mortality of allograft pancreatectomy, and emphasize the benefits of early retransplantation in appropriate candidates[47]. However, late pancreas retransplantation is also possible, although it has been associated with poorer allograft survival[48], in recent series technical failure and patient death for primary *vs* pancreas retransplants are similar in highly selected patients, if they are carried out in experienced centers[49-51].

Surgical technique

In cases of early transplantectomy, adhesions are not usually a problem. In order to gain rapid exposure of the vascular anastomoses, it is helpful to divide the enteric anastomosis first using a gastrointestinal anastomosis stapler by resecting the jejunum segment together with the duodenum (in enteric drainage transplants). The portal vein and iliac artery of the graft are clamped, divided, and oversewn. And then, the intestinal transit is reestablished with a jejunal anastomosis.

In cases of late transplantectomy, it can be performed in isolation or associated with a pancreas retransplantation. The operative field can be complex due to the adhesions, and in many occasions the graft will be shrunken, fibrosed, and poorly perfused, and there may be extensive adhesions to the retroperitoneum, making it difficult to identify. When graft pancreatectomy is performed as an isolated operation, the complete exposure of the recipient vasculature is often unnecessary. But when a failed allograft is removed at the time of retransplantation, the initial pancreas graft must be carefully explored and dissected away from the recipient iliac vessels and the inferior vena cava, in order to identify appropriate sites for implantation of the new pancreas graft. The allograft portal vein and iliac artery, once identified, are divided and oversewn taking care to avoid compromising the recipient arterial lumen. In cases where is not possible to preserve the recipient iliac vessels blood flow due to their involvement, as in PA or arterioenteric fistulas, an endovascular placement of a covered stent can be placed at the level of the anastomotic site. Alternatively, if it is not effective, an angioplasty with bovine pericardial patch can be done in cases of small defects of the vessel wall. Otherwise, a reconstruction with a synthetic prosthesis or

cadaver graft if available in cases of major vessel damage is a valid option[52].

CONCLUSION

Pancreas transplantation is a complex and technically demanding procedure. Early complications may occur, mostly due to technical failure as thrombosis, intraabdominal infections and pancreatitis. But late complications also entail a high percentage of graft losses, particularly secondary to chronic rejection or even late infections. PA are uncommon, but one of the main causes of late bleeding, which can be fatal. A high index of suspicion is needed to detect it, and once PA is diagnosed, the treatment should be performed, preferably with radiological endovascular approaches or open surgery in case of failure. Despite all therapeutic options for the complications mentioned above, transplantectomy is necessary in approximately 50% of relaparotomies, especially in life-threatening complications. Although pancreas retransplantation can be performed later in selected patients. Close monitoring of graft function and clinical and radiological surveillance, as well as new advances in the immunosuppression protocols, individualized according to the patient´s situation are crucial to prevent rejection, improving pancreas graft survival, as well as the optimal control of cardiovascular comorbidity to achieve better patient long-term survival.

REFERENCES

1 **Dean PG**, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. *BMJ* 2017; **357**: j1321 [PMID: 28373161 DOI: 10.1136/bmj.j1321]

2 **Kandaswamy R**, Stock PG, Gustafson SK, Skeans MA, Urban R, Fox A, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Pancreas. *Am J Transplant* 2020; **20** Suppl s1: 131-192 [PMID: 31898415 DOI: 10.1111/ajt.15673]

3 **Rickels MR**, Stock PG, de Koning EJP, Piemonti L, Pratschke J, Alejandro R, Bellin MD, Berney T, Choudhary P, Johnson PR, Kandaswamy R, Kay TWH, Keymeulen B, Kudva YC, Latres E, Langer RM, Lehmann R, Ludwig B, Markmann JF, Marinac M, Odorico JS, Pattou F, Senior PA, Shaw JAM, Vantyghem MC, White S. Defining outcomes for β-cell replacement therapy in the treatment of diabetes: a consensus report on the Igls criteria from the IPITA/EPITA opinion leaders workshop. *Transpl Int* 2018; **31**: 343-352 [PMID: 29453879 DOI: 10.1111/tri.13138]

4 **Jiménez-Romero C**, Marcacuzco Quinto A, Manrique Municio A, Justo Alonso I, Calvo Pulido J, Cambra Molero F, Caso Maestro Ó, García-Sesma Á, Moreno González E. Simultaneous pancreas-kidney transplantation. Experience of the Doce de Octubre Hospital. *Cir Esp* 2018; **96**: 25-34 [PMID: 29089105 DOI: 10.1016/j.ciresp.2017.09.016]

5 **Gruessner AC**, Gruessner RW. Long-term outcome after pancreas transplantation: a registry analysis. *Curr Opin Organ Transplant* 2016; **21**: 377-385 [PMID: 27258580 DOI: 10.1097/MOT.0000000000000331]

6 **Grochowiecki T**, Gałązka Z, Madej K, Frunze S, Nazarewski S, Jakimowicz T, Paczek L, Durlik M, Szmidt J. Multivariate analysis of complications after simultaneous pancreas and kidney transplantation. *Transplant Proc* 2014; **46**: 2806-2809 [PMID: 25380923 DOI: 10.1016/j.transproceed.2014.08.010]

7 **Herrero-Martínez JM**, Lumbreras C, Manrique A, San-Juan R, García-Reyne A, López-Medrano F, Lizasoain M, de Dios B, Andrés A, Jiménez C, Gutiérrez E, Moreno E, Aguado JM. Epidemiology, risk factors and impact on long-term pancreatic function of infection following pancreas-kidney transplantation. *Clin Microbiol Infect* 2013; **19**: 1132-1139 [PMID: 23480521 DOI: 10.1111/1469-0691.12165]

8 **Montero N**, Webster AC, Royuela A, Zamora J, Crespo Barrio M, Pascual J. Steroid avoidance or withdrawal for pancreas and pancreas with kidney transplant recipients. *Cochrane Database Syst Rev* 2014; : CD007669 [PMID: 25220222 DOI: 10.1002/14651858.CD007669.pub2]

9 **Heilman RL**, Mazur MJ, Reddy KS. Immunosuppression in simultaneous pancreas-kidney transplantation: progress to date. *Drugs* 2010; **70**: 793-804 [PMID: 20426494 DOI: 10.2165/11535430-000000000-00000]

10 **Ciancio G**, Sageshima J, Chen L, Gaynor JJ, Hanson L, Tueros L, Montenora-Velarde E, Gomez C, Kupin W, Guerra G, Mattiazzi A, Fornoni A, Pugliese A, Roth D, Wolf M, Burke GW 3rd. Advantage of rapamycin over mycophenolate mofetil when used with tacrolimus for simultaneous pancreas kidney transplants: randomized, single-center trial at 10 years. *Am J Transplant* 2012; **12**: 3363-3376 [PMID: 22946986 DOI: 10.1111/j.1600-6143.2012.04235.x]

11 **Marcella-Neto R**, de Sá JR, Melaragno CS, Gonzalez AM, Salzedas-Neto A, Linhares MM, Medina-Pestana JO, Rangel ÉB. Late Conversion to Sirolimus or Everolimus After Pancreas Transplant. *Transplant Proc* 2020; **52**: 1376-1379 [PMID: 32213293 DOI: 10.1016/j.transproceed.2020.02.028]

12 **Kudva YC**, Erickson JR, Parsaik A, Rostambeigi N, Thapa P, Abraham RS. Comprehensive immune monitoring reveals profound immunological changes in pancreas after kidney (PAK) transplant

recipients. *Hum Immunol* 2013; **74**: 738-745 [PMID: 23474226 DOI: 10.1016/j.humimm.2013.02.004]

13 **Humar A**, Khwaja K, Ramcharan T, Asolati M, Kandaswamy R, Gruessner RW, Sutherland DE, Gruessner AC. Chronic rejection: the next major challenge for pancreas transplant recipients. *Transplantation* 2003; **76**: 918-923 [PMID: 14508354 DOI: 10.1097/01.TP.0000079457.43199.76]

14 **Wakil K**, Sugawara Y, Kokudo N, Kadowaki T. Causes of graft failure in simultaneous pancreas-kidney transplantation by various time periods. *Clin Transpl*2013: 23-30 [PMID: 25095489]

15 **O'Malley RB**, Moshiri M, Osman S, Menias CO, Katz DS. Imaging of Pancreas Transplantation and Its Complications. *Radiol Clin North Am* 2016; **54**: 251-266 [PMID: 26896223 DOI: 10.1016/j.rcl.2015.09.012]

16 **Lee BC**, McGahan JP, Perez RV, Boone JM. The role of percutaneous biopsy in detection of pancreatic transplant rejection. *Clin Transplant* 2000; **14**: 493-498 [PMID: 11048995 DOI: 10.1034/j.1399-0012.2000.140508.x]

17 **Drachenberg CB**, Odorico J, Demetris AJ, Arend L, Bajema IM, Bruijn JA, Cantarovich D, Cathro HP, Chapman J, Dimosthenous K, Fyfe-Kirschner B, Gaber L, Gaber O, Goldberg J, Honsová E, Iskandar SS, Klassen DK, Nankivell B, Papadimitriou JC, Racusen LC, Randhawa P, Reinholt FP, Renaudin K, Revelo PP, Ruiz P, Torrealba JR, Vazquez-Martul E, Voska L, Stratta R, Bartlett ST, Sutherland DE. Banff schema for grading pancreas allograft rejection: working proposal by a multi-disciplinary international consensus panel. *Am J Transplant* 2008; **8**: 1237-1249 [PMID: 18444939 DOI: 10.1111/j.1600-6143.2008.02212.x]

18 **Drachenberg CB**, Torrealba JR, Nankivell BJ, Rangel EB, Bajema IM, Kim DU, Arend L, Bracamonte ER, Bromberg JS, Bruijn JA, Cantarovich D, Chapman JR, Farris AB, Gaber L, Goldberg JC, Haririan A, Honsová E, Iskandar SS, Klassen DK, Kraus E, Lower F, Odorico J, Olson JL, Mittalhenkle A, Munivenkatappa R, Paraskevas S, Papadimitriou JC, Randhawa P, Reinholt FP, Renaudin K, Revelo P, Ruiz P, Samaniego MD, Shapiro R, Stratta RJ, Sutherland DE, Troxell ML, Voska L, Seshan SV, Racusen LC, Bartlett ST. Guidelines for the diagnosis of antibody-mediated rejection in pancreas allografts-updated Banff grading schema. *Am J Transplant* 2011; **11**: 1792-1802 [PMID: 21812920 DOI: 10.1111/j.1600-6143.2011.03670.x]

19 **Argente-Pla M**, Martínez-Millana A, Del Olmo-García MI, Espí-Reig J, Pérez-Rojas J, Traver-Salcedo V, Merino-Torres JF. Autoimmune Diabetes Recurrence After Pancreas Transplantation: Diagnosis, Management, and Literature Review. *Ann Transplant* 2019; **24**: 608-616 [PMID: 31767825 DOI: 10.12659/AOT.920106]

20 **Burke GW 3rd**, Vendrame F, Virdi SK, Ciancio G, Chen L, Ruiz P, Messinger S, Reijonen HK, Pugliese A. Lessons From Pancreas Transplantation in Type 1 Diabetes: Recurrence of Islet Autoimmunity. *Curr Diab Rep* 2015; **15**: 121 [PMID: 26547222 DOI: 10.1007/s11892-015-0691-5]

21 **Kopp W**, van Meel M, Putter H, Samuel U, Arbogast H, Schareck W, Ringers J, Braat A. Center Volume Is Associated With Outcome After Pancreas Transplantation Within the Eurotransplant Region. *Transplantation* 2017; **101**: 1247-1253 [PMID: 27379557 DOI: 10.1097/TP.0000000000001308]

22 **Alhamad T**, Malone AF, Brennan DC, Stratta RJ, Chang SH, Wellen JR, Horwedel TA, Lentine KL. Transplant Center Volume and the Risk of Pancreas Allograft Failure. *Transplantation* 2017; **101**: 2757-2764 [PMID: 28099402 DOI: 10.1097/TP.0000000000001628]

23 **Kim Y**, Dhar VK, Wima K, Jung AD, Xia BT, Hoehn RS, Diwan TS, Shah SA. The center volume-outcome effect in pancreas transplantation: a national analysis. *J Surg Res* 2017; **213**: 25-31 [PMID: 28601322 DOI: 10.1016/j.jss.2017.02.025]

24 **Rostambeigi N**, Kudva YC, John S, Mailankody S, Pedersen RA, Dean PG, Prieto M, Cosio FG, Kremers WK, Walker RC, Abraham RS, Stegall MD. Epidemiology of infections requiring hospitalization during long-term follow-up of pancreas transplantation. *Transplantation* 2010; **89**: 1126-1133 [PMID: 20164817 DOI: 10.1097/TP.0b013e3181d54bb9]

25 **Helfrich M**, Dorschner P, Thomas K, Stosor V, Ison MG. A retrospective study to describe the epidemiology and outcomes of opportunistic infections after abdominal organ transplantation. *Transpl Infect Dis* 2017; **19** [PMID: 28273393 DOI: 10.1111/tid.12691]

26 **Anesi JA**, Blumberg EA, Abbo LM. Perioperative Antibiotic Prophylaxis to Prevent Surgical Site Infections in Solid Organ Transplantation. *Transplantation* 2018; **102**: 21-34 [PMID: 28614192 DOI: 10.1097/TP.0000000000001848]

27 **Wang EH**, Partovi N, Levy RD, Shapiro RJ, Yoshida EM, Greanya ED. Pneumocystis pneumonia in solid organ transplant recipients: not yet an infection of the past. *Transpl Infect Dis* 2012; **14**: 519-525 [PMID: 22571389 DOI: 10.1111/j.1399-3062.2012.00740.x]

28 **Kotton CN**, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, Humar A; The Transplantation Society International CMV Consensus Group. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. *Transplantation* 2018; **102**: 900-931 [PMID: 29596116 DOI: 10.1097/TP.0000000000002191]

29 **Fallatah SM**, Marquez MA, Bazerbachi F, Schiff JR, Cattral MS, McGilvray ID, Norgate A, Selzner M, Rotstein C, Husain S. Cytomegalovirus infection post-pancreas-kidney transplantation--results of antiviral prophylaxis in high-risk patients. *Clin Transplant* 2013; **27**: 503-509 [PMID: 23731387 DOI: 10.1111/ctr.12138]

30 **Kotton CN**. Updates on antiviral drugs for cytomegalovirus prevention and treatment. *Curr Opin Organ Transplant* 2019; **24**: 469-475 [PMID: 31157669 DOI: 10.1097/MOT.0000000000000666]

31 **Mallat SG**, Tanios BY, Itani HS, Lotfi T, McMullan C, Gabardi S, Akl EA, Azzi JR. CMV and

BKPyV Infections in Renal Transplant Recipients Receiving an mTOR Inhibitor-Based Regimen Versus a CNI-Based Regimen: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. *Clin J Am Soc Nephrol* 2017; **12**: 1321-1336 [PMID: 28576905 DOI: 10.2215/CJN.13221216]

32 **Karpe KM**, Talaulikar GS, Walters GD. Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients. *Cochrane Database Syst Rev* 2017; **7**: CD006750 [PMID: 28730648 DOI: 10.1002/14651858.CD006750.pub2]

33 **Meije Y**, Piersimoni C, Torre-Cisneros J, Dilektasli AG, Aguado JM; ESCMID Study Group of Infection in Compromised Hosts. Mycobacterial infections in solid organ transplant recipients. *Clin Microbiol Infect* 2014; **20** Suppl 7: 89-101 [PMID: 24707957 DOI: 10.1111/1469-0691.12641]

34 **Bratton CF**, Hamid A, Selby JB, Baliga PK. Case report: gastrointestinal hemorrhage caused by a pancreas transplant arteriovenous fistula with large psuedoanuerysm 9 years after transplantation. *Transplant Proc* 2011; **43**: 4039-4043 [PMID: 22172898 DOI: 10.1016/j.transproceed.2011.09.071]

35 **Morelli L**, Di Candio G, Campatelli A, Vistoli F, Del Chiaro M, Balzano E, Croce C, Moretto C, Signori S, Boggi U, Mosca F. Role of color Doppler sonography in post-transplant surveillance of vascular complications involving pancreatic allografts(). *J Ultrasound* 2008; **11**: 18-21 [PMID: 23396980 DOI: 10.1016/j.jus.2007.10.003]

36 **Surowiecka-Pastewka A**, Matejak-Górska M, Frączek M, Sklinda K, Walecki J, Durlik M. Endovascular Interventions in Vascular Complications After Simultaneous Pancreas and Kidney Transplantations: A Single-Center Experience. *Ann Transplant* 2019; **24**: 199-207 [PMID: 30975974 DOI: 10.12659/AOT.912005]

37 **Yadav K**, Young S, Finger EB, Kandaswamy R, Sutherland DER, Golzarian J, Dunn TB. Significant arterial complications after pancreas transplantation-A single-center experience and review of literature. *Clin Transplant* 2017; **31** [PMID: 28787529 DOI: 10.1111/ctr.13070]

38 **Montenovo M**, Vaidya S, Bakthavatsalam R, Halldorson J. Pseudoaneurysm after combined kidney/pancreas transplantation presenting with sentinel bleeding: a case report and review. *Ann Transplant* 2014; **19**: 317-319 [PMID: 24995594 DOI: 10.12659/AOT.890356]

39 **Buttarelli L**, Capocasale E, Marcato C, Mazzoni MP, Iaria M, Rossi C. Embolization of pancreatic allograft arteriovenous fistula with the Amplatzer Vascular Plug 4: case report and literature analysis. *Transplant Proc* 2011; **43**: 4044-4047 [PMID: 22172899 DOI: 10.1016/j.transproceed.2011.08.099]

40 **Huurman VAL**, Lardenoye JHP. Pancreas graft salvage after successful endovascular treatment of Y graft pseudoaneurysm. *J Surg Case Rep* 2019; **2019**: rjz124 [PMID: 31110652 DOI: 10.1093/jscr/rjz124]

41 **Kurose S**, Inoue K, Yoshino S, Nakayama K, Yamashita S, Yoshiya K, Yoshiga R, Morisaki K, Kaku K, Okabe Y, Furuyama T, Maehara Y. Successful Bridge Therapy with Initial Endovascular Repair for Arterioenteric Fistula Resulting from Pseudoaneurysm Rupture with Massive Gastrointestinal Hemorrhage after Pancreas Transplantation. *Ann Vasc Surg* 2019; **58**: 379.e15-379. e22 [PMID: 30711503 DOI: 10.1016/j.avsg.2018.10.028]

42 **Arantes RM**, Pantanali CA, Santos VR, Carneiro D'Albuquerque LA. Arterial Pseudoaneurysm Associated with Pancreas and Kidney Transplantation: A Case Report. *Am J Case Rep* 2017; **18**: 198-202 [PMID: 28232659 DOI: 10.12659/ajcr.900790]

43 **Patrono D**, Verhelst R, Buemi A, Darius T, Godefroid N, Mourad M. Presentation and management of mycotic pseudoaneurysm after kidney transplantation. *Transpl Infect Dis* 2015; **17**: 129-136 [PMID: 25620391 DOI: 10.1111/tid.12346]

44 **Manrique A**, Jiménez C, López RM, Cambra F, Morales JM, Andrés A, Gutiérrez E, Ortuño T, Calvo J, Sesma AG, Moreno E. Relaparotomy after pancreas transplantation: causes and outcomes. *Transplant Proc* 2009; **41**: 2472-2474 [PMID: 19715955 DOI: 10.1016/j.transproceed.2009.06.165]

45 **Parajuli S**, Odorico J, Astor BC, Djamali A, Sollinger H, Redfield R, Kaufman D, Mandelbrot DA. Incidence and Indications for Late Allograft Pancreatectomy While on Continued Immunosuppression. *Transplantation* 2017; **101**: 2228-2234 [PMID: 27798517 DOI: 10.1097/TP.0000000000001556]

46 **Nagai S**, Powelson JA, Taber TE, Goble ML, Mangus RS, Fridell JA. Allograft Pancreatectomy: Indications and Outcomes. *Am J Transplant* 2015; **15**: 2456-2464 [PMID: 25912792 DOI: 10.1111/ajt.13287]

47 **Hollinger EF**, Powelson JA, Mangus RS, Kazimi MM, Taber TE, Goble ML, Fridell JA. Immediate retransplantation for pancreas allograft thrombosis. *Am J Transplant* 2009; **9**: 740-745 [PMID: 19298453 DOI: 10.1111/j.1600-6143.2009.02517.x]

48 **Siskind E**, Maloney C, Jayaschandaran V, Kressel A, Akerman M, Shen A, Amodu L, Platz J, Ricci JP, Bhaskaran M, Basu A, Molmenti E, Ortiz J. Pancreatic retransplantation is associated with poor allograft survival: an update of the United Network for Organ Sharing database. *Pancreas* 2015; **44**: 769-772 [PMID: 25931257 DOI: 10.1097/MPA.0000000000000330]

49 **Perosa M**, Sergi F, Noujaim H. Outcomes after pancreas retransplantation: is the juice worth the squeeze? *Curr Opin Organ Transplant* 2018; **23**: 461-466 [PMID: 29979264 DOI: 10.1097/MOT.0000000000000554]

50 **Gasteiger S**, Cardini B, Göbel G, Oberhuber R, Messner F, Resch T, Bösmüller C, Margreiter C, Schneeberger S, Maglione M. Outcomes of pancreas retransplantation in patients with pancreas graft failure. *Br J Surg* 2018; **105**: 1816-1824 [PMID: 30007018 DOI: 10.1002/bjs.10929]

51 **Rudolph EN**, Finger EB, Chandolias N, Kandaswamy R, Sutherland DE, Dunn TB. Outcomes of pancreas retransplantation. *Transplantation* 2015; **99**: 367-374 [PMID: 25594555 DOI: 10.1097/TP.0000000000000566]

52 **Laurence JM**, Cattral MS. Techniques of pancreas graft salvage/indications for allograft pancreatectomy. *Curr Opin Organ Transplant* 2016; **21**: 405-411 [PMID: 27058314 DOI: 10.1097/MOT.0000000000000318]

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MINIREVIEWS

Immediate post-operative complications (I): Post-operative bleeding; vascular origin: Thrombosis pancreatitis

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Abstract

Simultaneous pancreas-kidney transplantation is the treatment of choice for insulin-dependent diabetes that associates end-stage diabetic nephropathy, since it achieves not only a clear improvement in the quality of life, but also provides a long-term survival advantage over isolated kidney transplant. However, pancreas transplantation still has the highest rate of surgical complications among organ transplants. More than 70% of early graft losses are attributed to technical failures, that is, to a non-immunological cause. The so-called technical failures include graft thrombosis, bleeding, infection, pancreatitis, anastomotic leak and pancreatic fistula. Pancreatic graft thrombosis leads these technical complications as the most frequent cause of early graft loss. Currently most recipients receive postoperative anticoagulation with the aim of reducing the rate of thrombosis. Hemoperitoneum in the early postoperative period is a frequent cause of relaparotomy, but it is not usually associated with graft loss. The incidence of hemoperitoneum is clearly related to the use of anticoagulation in the postoperative period. Post-transplant pancreatitis is another cause of early postoperative complications, less frequent than the previous. In this review, we analyze the most common surgical complications that determine pancreatic graft losses.

Key Words: Pancreas transplantation; Vascular graft thrombosis; Postoperative hemorrhage; Graft pancreatitis; Reperfusion injury; Tissue donors; Risk factors

Core Tip: Pancreas transplantation still has the highest rate of surgical complications among all solid organ transplants. Pancreatic graft thrombosis leads these technical complications as the leading cause of early pancreatic graft loss. Hemoperitoneum in the early postoperative period frequently requires a relaparotomy, but usually it is not

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associated with graft loss. Severe pancreatitis is a major complication because it is associated with infection and can lead to graft loss.

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INTRODUCTION

Pancreas transplantation still has the highest rate of surgical complications among all solid organ transplants. More than 70% of early pancreatic graft losses are attributed to technical failures, that means, attributed to a non-immunological cause.

The so-called technical failures include graft thrombosis, bleeding, infection, pancreatitis, anastomotic leak and pancreatic fistula.

Pancreatic graft thrombosis leads these technical complications as the most frequent cause of early pancreatic graft loss[1].

PANCREATIC ALLOGRAFT THROMBOSIS

Vascular thrombosis, including venous and arterial thrombosis, is one of the most severe complications following pancreas transplantation, since it continues to contribute significantly to early graft failure and loss. Thrombosis can be partial or total. Venous thrombosis has a higher incidence than arterial thrombosis (3:1)[2]. The incidence of complete allograft thrombosis provided in the literature ranges from 3% to 10%[1,2], while partial thrombosis incidence can be as high as 25%-30%[1,3,4].

Early thrombosis occurs within the first 6 wk after the transplant, although it is more common in the first week and generally within the first 48 h after the surgery[5].

Early complete venous graft thrombosis manifests as hyperglycaemia, abdominal pain over the area where the graft is located, plus melena when the drainage is enteric or haematuria and decrease in urinary-amylase production when the drainage is to the bladder. Arterial thrombosis does not express bleeding data. The suspected diagnosis is confirmed with doppler ultrasound[6] and the extension of the thrombosis is assessed by computed tomography (CT) angiography, providing the necessary information to plan the best individualized treatment for each patient. Reintervention and pancreatectomy may be the best option on many occasions and explains the importance of this complication among early graft losses. The reasons why there is a greater tendency to thrombosis in pancreas transplantation, compared to other solid organ transplants, are diverse and probably multifactorial. Predisposing factors are still not well understood but include the hypercoagulable state of patients with diabetic renal failure, preservation-related graft endothelial injury and low velocity venous flow. Regarding to the pathophysiology, diabetes itself triggers a state of hypercoagulability. The decrease of the blood supply to the great vessels that allow the irrigation and venous drainage of the transplanted pancreatic graft is also proposed as a remarkable prothrombotic factor. In fact, the flow in the portal vein usually is 25% of cardiac output, around 1 L/min. The flow in the transplanted pancreas is approximately 150 mL/min, and it can be even lower if some degree of post-transplant pancreatitis occurs[7]. This striking decrease in the flow of the splenic vein, mesenteric superior vein and portal vein results in a clear prothrombotic situation.

Endothelial damage related to ischemia-reperfusion phenomenon and post-transplantation pancreatitis also play an important role, as demonstrated by the linear association between cold ischemia time and thrombosis rate[7].

Donor risk factors associated with graft thrombosis are, as expected, similar to those described in the University of Minnesota study[2] about early graft loss: (1) Donor obesity, expressed as a body mass index (BMI) higher than 30 kg/m^2; (2) Donor age > 50 years old; (3) Cerebrovascular cause of death, highly correlated with age; (4) Donor Creatinine > 2.5 mg/dL; (5) Donors after circulatory death (Maastricht 2 and 3). Preliminary reports of donors with cardiac death show a substantially higher

thrombosis rate compared to donors after brain death; and (6) Total ischemia time > 20 h. There are studies that lower this ischemia time limit to > 12 h when preservation fluids other than Wisconsin are used, such as Custodiol.

Therefore, it is not surprising that the scoring systems available that attempt to assess the suitability of a pancreas donor, such as the preprocurement pancreas score and the donor risk index pancreas (PDRI), demonstrate greater incidence of thrombosis and graft loss in older donors with a higher BMI. The PDRI developed by Axelrod *et al*[8] measures the risk of organs based on 10 donor factors, such as age, BMI and cause of death, and only 1 recipient factor, the cold ischemia time. Higher PDRI correlates with higher rates of technical failure and significantly lower 1-year graft survival rates, particularly in the pancreas after kidney transplant and in isolated pancreas transplantation. The PDRI was developed after the statistical analysis of the pancreatic transplant data from the united network for organ sharing registry in the United States and has been validated in the United Kingdom for Simultaneous pancreas-kidney transplantation.

The recipient-related thrombosis risk factors are less clear. Advanced arteriosclerotic disease in the recipient is usually an exclusion criterion for pancreas transplantation due to an increased risk of arterial thrombosis. However, recipient's obesity increases the overall risk of surgical complications, such as enteric leakage, hernia or infections, but it does not increase the thrombosis rate[1]. Hereditary thrombophilic disorders can be added to recipient's risk factors, including deficiencies of natural anticoagulants such as antithrombin, protein C and protein S, and genetic mutations such as factor V Leiden and prothrombin mutations that also contribute to an increase in risk of thrombosis. These inherited thrombophilic disorders specifically increase the risk of venous thrombosis and have a cumulative effect with other risk factors[9,10]. To sum up, the greater tendency to thrombosis in pancreas transplantation is not due to a single cause but rather it is a multifactorial process that includes characteristics of the donor, extraction technique, type of preservation fluid, characteristics of the recipients, surgical technique during the implant and anticoagulant therapy used (Table 1).

Clinical management

Therapeutic interventions aimed to reduce thrombotic graft loss can be classified: (1) Prophylactic measures; (2) Early detection, graft surveillance; and (3) Intervention procedures aimed at saving the thrombosed graft.

Prophylaxis: Majority of transplant centers have adopted some type of routine prophylactic anticoagulation with various combinations of aspirin, unfractionated heparin, low molecular weight heparin and warfarin, with variable results but generally beneficial reducing the incidence of thrombosis[4].

There is currently no standard protocol consistently proven to prevent thrombosis following transplantation.

This prophylactic anticoagulation justifies that hemoperitoneum is the leading cause of surgical reintervention in the early postoperative period after pancreas transplantation.

Surveillance: Blood glucose monitoring in the early post-transplant period is especially useful to warn us about a possible vascular complication. Doppler ultrasound, CT angiography and magnetic resonance imaging (MRI) angiography have been used effectively in the early diagnosis of vascular graft complications. It is usual to perform imaging controls during the first days after pancreas transplantation with Doppler ultrasound[5]. If thrombosis is suspected, CT angiography or MRI angiography is performed to confirm the diagnosis and propose therapeutic options.

There are teams that perform CT angiography routinely in the early post-transplant period. These groups report higher thrombosis rates, including partial and asymptomatic thrombosis, which might not be detected with Doppler ultrasound[4-6].

Intervention: Partial venous thrombosis (usually of the splenic vein) has been managed successfully only with complete therapeutic anticoagulation[11,12]. However, complete portal thrombosis usually results in graft loss, although successful surgical and radiological rescues have been reported[13-16]. Radiological surveillance is critical in the early diagnosis of partial thrombosis, which can often be saved by therapeutic anticoagulation.

Due to the change in the donors profile, more transplants are currently performed with risk factors known as age, obesity, stroke as the cause of death and the donor in asystole. In this type of expanded donors, it is important not to add any more risk factors during the extraction, minimize the ischemia time and discard high thrombotic risk recipients detected during the pre-transplant evaluation, mainly thrombophilia,

Table 1 Summarizes these risk factors

Thrombosis risk factor in pancreas transplantation
Donor
Donor > 50 years old
Cerebrovascular cause of death
Prolonged cardiac arrest in the donor
Donors after circulatory death (Maastrich 2 and 3)
Prolonged hypotension periods
Obesity
Important arteriosclerosis in the celiac trunk
Extraction and preservation of pancreas:
Vascular abnormalities
Vascular injury during extraction (dorsal pancreatic artery)
Preservation solution (type, volume and perfusion pressure)
Ischemia time (warm and cold)
Recipient:
Severe arteriosclerosis in the iliac vessels
Age > 55 years old
Isolated transplant or pancreas transplant after kidney
Anticoagulant therapy established
Thrombophilia

advanced arteriosclerosis and pancreas alone transplant.

HEMORRHAGE

Unlike other abdominal transplants, such as liver or kidney transplants, in which reoperations are rare, pancreas transplantation is subjected to a high rate of reoperations, which can be as high as 30%. Hemoperitoneum is the most frequent cause of reoperation in the immediate postoperative period[3]. Fortunately, this event does not significantly affect graft survival. Bleeding represents less than 0.3% of early pancreatic graft losses. The incidence of hemoperitoneum is clearly related to the use of anticoagulation in the postoperative period. We need to distinguish between intra-abdominal, digestive and bladder haemorrhage.

Intra-abdominal haemorrhage

Most of the important hemoperitoneum that occurs in the early postoperative period has a surgical cause, in relation to peripancreatic vessels or vascular anastomosis, enhanced by the antithrombotic prophylaxis[17]. The meticulous preparation of the duodenopancreatic graft during bench surgery can help to prevent most of these bleedings.

Once intra-abdominal bleeding has been diagnosed, we must correct any coagulation abnormality and suspend prophylactic heparin. If bleeding persists, surgical exploration would be indicated. In a recipient with hemodynamic instability we should not delay relaparotomy.

Possible causes of late intra-abdominal haemorrhage are ruptures of a fungal pseudoaneurysm, rupture of an arterial aneurysm or an arteriovenous fistula. The treatment of choice is endovascular, either by embolization or by stent[18].

Digestive haemorrhage

Early digestive bleeding usually comes from the digestive anastomosis or the staple line of the duodenal ends. They are usually self-limited bleeding that responds to

conservative measures (correction of coagulation abnormalities, heparin withdrawal and transfusion). If conservative measures do not solve the bleeding, the surgical revision is indicated.

Bladder haemorrhage

Early post-transplant haematuria is common in patients with bladder drainage and it is usually self-limited. In some cases, it is necessary to establish a continuous irrigation of the bladder.

PANCREATITIS

Early pancreatitis after a pancreas transplant occurs in 10%-20% of patients[19]. It is specially associated to ischemia-reperfusion damage to the transplanted organ. Other less frequent causes involved are acute rejection and technical problems, especially if they affect ductal integrity[7].

High serum amylase levels and graft edema are characteristic. Most ischemia-reperfusion pancreatitis are mild and progress favourably in the first days of the postoperative period. From an analytical point of view, the serum amylase peak due to ischemia-reperfusion damage occurs within the first 24-48 h after transplantation and rapidly evolves towards normalization[20].

Regarding to imaging tests (CT and MRI), most recipients present in the immediate post-transplant period signs of mild pancreatitis that include graft enlargement, a thin ring of peripancreatic fluid and minimal peripancreatic fat infiltration.

Pancreatitis due to acute rejection usually results in a later elevation of serum amylase, from the fifth day after the transplantation. They are usually accompanied by data on acute rejection in the renal graft. The intensification of immunosuppression controls these immunological pancreatitis in most cases.

Complications of severe graft pancreatitis include pancreatic abscesses, sterile or infected pancreatic necrosis, pancreatic fistulas and pseudocysts. Severe pancreatitis is an important complication not only because it is commonly associated with infection, but also because it is a major risk factor for graft thrombosis[7].

Currently, graft losses associated with severe pancreatitis and its complications do not exceed 0.6% of pancreas transplants.

However, determining the true incidence of severe graft pancreatitis is difficult because of the lack of a commonly accepted definition. There is not a classification for graft thrombosis, like Atlanta classification for native pancreatitis.

Another key point is that severe pancreatitis is frequently associated with infection and it is difficult to determine which one of this two complications appeared first. The united network for organ sharing Pancreas Transplant Registry does not even name pancreatitis as a separate cause of technical failure itself, but along with infection.

Risk factors for pancreatitis include donor risk factors (hemodynamic instability, vasopressor administration, obesity, age), injuries during multiorgan extraction, reperfusion damages (excessive volume infusion or excessive perfusion pressure), preservation injuries associated with an extended preservation time.

Although relatively rare, technical surgical problems can cause narrowing of the pancreatic duct. Another cause that produces obstruction of the pancreatic duct is urinary reflux when we use a bladder drainage. Rarer causes of pancreatitis include complications of a biopsy or bacterial and viral infections (for example cytomegalovirus).

Graft pancreatitis is suspected when elevated serum amylase and lipase are detected, and the recipient complains of abdominal pain where the graft is located. In severe pancreatitis, patients usually present other clinical symptoms like nausea, vomiting and ileus.

In some cases of graft pancreatitis, recipients may be hemodynamically instable and may even develop an adult respiratory distress syndrome. In grafts with bladder drainage, urinary amylase decreases markedly during episodes of pancreatitis. However, the endocrine graft function is often preserved, even in cases of severe pancreatitis, and only requires exogenous insulin when parenteral nutrition is administered.

The severity of pancreatitis is defined by laboratory data, including leukocytosis, hypocalcemia and elevated C-reactive protein. The degree of pancreatic inflammation or necrosis is assessed with abdominal CT. Abdominal MRI is less useful than CT in this contex.

The treatment of pancreatitis is dictated by the treatment of the underlying cause.

Severe ischemia-reperfusion pancreatitis is usually treated with intestinal rest and nasogastric tube placement. Occasionally, parenteral nutrition is necessary. The use of octreotide to treat post-transplant pancreatitis has been suggested, but there is no clear evidence of its benefit. In cases of severe graft pancreatitis that endanger the patient's life, due to the association of serious complications such as adult respiratory distress syndrome or septic shock, graft pancreatectomy is indicated. When pancreatic duct obstruction is the cause of the pancreatitis, a reoperation is required, and it will frequently be necessary to perform a pancreatectomy.

Reflux pancreatitis in recipients with bladder drainage is easily diagnosed and treated with the placement of a foley catheter. Repeated episodes of reflux pancreatitis in recipients with bladder drainage, is an indication of conversion to enteric drainage. Any peripancreatic infection associated with pancreatitis (*e.g.*, peripancreatic abscess) has an indication of interventional radiology drainage, as well as an adequate antibiotic treatment.

Given the complications associated with severe acute graft pancreatitis, it is important to reduce its incidence by avoiding the known risk factors of the donor, mainly hemodynamic instability and obesity, as well as reducing the graft ischemia time as much as possible.

CONCLUSION

In this review we analyze three of the most important and frequent complications that occur in the early postoperative period after pancreas transplantation.

Thrombosis justifies most of early graft losses. Performing a detailed surgical technique, minimizing risk factors in the donor and recipient, as well as using the appropriate antithrombotic protocol can lead to minimize the rate of thrombosis.

Postoperative haemorrhage justifies most of the reoperations but does not usually trigger graft loss. A balance needs to be struck between anticoagulation to prevent graft thrombosis and a reasonable reoperation rate. Meticulous haemostasis at the end of the procedure is essential to decrease the bleeding rate.

Finally, posttransplant pancreatitis, usually mild, related to ischemia-reperfusion, usually has a favorable course. A small percentage associates reoperations and graft loss. Minimizing the ischemic time and avoiding associating risk factors reduces its incidence.

REFERENCES

1 **Finger EB**, Radosevich DM, Dunn TB, Chinnakotla S, Sutherland DE, Matas AJ, Pruett TL, Kandaswamy R. A composite risk model for predicting technical failure in pancreas transplantation. *Am J Transplant* 2013; **13**: 1840-1849 [PMID: 23711225 DOI: 10.1111/ajt.12269]

2 **Troppmann C**. Complications after pancreas transplantation. *Curr Opin Organ Transplant* 2010; **15**: 112-118 [PMID: 20009931 DOI: 10.1097/MOT.0b013e3283355349]

3 **Kopp WH**, van Leeuwen CAT, Lam HD, Huurman VAL, de Fijter JW, Schaapherder AF, Baranski AG, Braat AE. Retrospective study on detection, treatment, and clinical outcome of graft thrombosis following pancreas transplantation. *Transpl Int* 2019; **32**: 410-417 [PMID: 30525250 DOI: 10.1111/tri.13384]

4 **Hakeem A**, Chen J, Iype S, Clatworthy MR, Watson CJE, Godfrey EM, Upponi S, Saeb-Parsy K. Pancreatic allograft thrombosis: Suggestion for a CT grading system and management algorithm. *Am J Transplant* 2018; **18**: 163-179 [PMID: 28719059 DOI: 10.1111/ajt.14433]

5 **Muthusamy AS**, Giangrande PL, Friend PJ. Pancreas allograft thrombosis. *Transplantation* 2010; **90**: 705-707 [PMID: 20616765 DOI: 10.1097/TP.0b013e3181eb2ea0]

6 **Morgan TA**, Smith-Bindman R, Harbell J, Kornak J, Stock PG, Feldstein VA. US Findings in Patients at Risk for Pancreas Transplant Failure. *Radiology* 2016; **280**: 281-289 [PMID: 26807892 DOI: 10.1148/radiol.2015150437]

7 **Montiel-Casado MC**, Fernández-Burgos I, Pérez-Daga JA, Aranda-Narváez JM, Sánchez-Pérez B, González-Sánchez AJ, Cabello-Diaz M, Burgos-Rodríguez D, Hernández-Marrero D, Santoyo-Santoyo J. Impact of blood amylase peak over vascular graft thrombosis in pancreas transplantation. *Transplant Proc* 2012; **44**: 2627-2630 [PMID: 23146477 DOI: 10.1016/j.transproceed.2012.09.103]

8 **Axelrod DA**, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant* 2010; **10**: 837-845 [PMID: 20121753 DOI: 10.1111/j.1600-6143.2009.02996.x]

9 **Fischereder M**, Göhring P, Schneeberger H, Lohse P, Von Appen K, Samtleben W, Schlöndorff D, Land W. Early loss of renal transplants in patients with thrombophilia. *Transplantation* 1998; **65**: 936-939 [PMID: 9565098 DOI: 10.1097/00007890-199804150-00013]

10 **Adrogué HE**, Matas AJ, McGlennon RC, Key NS, Gruessner A, Gruessner RW, Humar A, Sutherland DE, Kandaswamy R. Do inherited hypercoagulable states play a role in thrombotic events affecting kidney/pancreas transplant recipients? *Clin Transplant* 2007; **21**: 32-37 [PMID: 17302589 DOI: 10.1111/j.1399-0012.2006.00574.x]

11 **Harbell JW**, Morgan T, Feldstein VA, Roll GR, Posselt A, Kang SM, Feng S, Hirose R, Freise CE, Stock P. Splenic Vein Thrombosis Following Pancreas Transplantation: Identification of Factors That Support Conservative Management. *Am J Transplant* 2017; **17**: 2955-2962 [PMID: 28707821 DOI: 10.1111/ajt.14428]

12 **Ciancio G**, Cespedes M, Olson L, Miller J, Burke GW. Partial venous thrombosis of the pancreatic allografts after simultaneous pancreas-kidney transplantation. *Clin Transplant* 2000; **14**: 464-471 [PMID: 11048991 DOI: 10.1034/j.1399-0012.2000.140504.x]

13 **Gilabert R**, Fernández-Cruz L, Real MI, Ricart MJ, Astudillo E, Montaña X. Treatment and outcome of pancreatic venous graft thrombosis after kidney--pancreas transplantation. *Br J Surg* 2002; **89**: 355-360 [PMID: 11872064 DOI: 10.1046/j.0007-1323.2001.02016.x]

14 **Fridell JA**, Mangus RS, Mull AB, Taber TE, Sanders CE, Slisher RC, Goble ML, Powelson JA. Early reexploration for suspected thrombosis after pancreas transplantation. *Transplantation* 2011; **91**: 902-907 [PMID: 21301398 DOI: 10.1097/TP.0b013e3182106069]

15 **Han K**, Ko HK, Tsauo J, Shim DJ, Kim Y, Ko GY, Han DJ, Shin S, Kim YH. Endovascular Management for the Treatment of Pancreas Transplant Venous Thrombosis: A Single-Center Experience. *J Vasc Interv Radiol* 2016; **27**: 882-888 [PMID: 27107981 DOI: 10.1016/j.jvir.2016.02.022]

16 **Laurence JM**, Cattral MS. Techniques of pancreas graft salvage/indications for allograft pancreatectomy. *Curr Opin Organ Transplant* 2016; **21**: 405-411 [PMID: 27058314 DOI: 10.1097/MOT.0000000000000318]

17 **Scheffert JL**, Taber DJ, Pilch NA, Chavin KD, Baliga PK, Bratton CF. Clinical outcomes associated with the early postoperative use of heparin in pancreas transplantation. *Transplantation* 2014; **97**: 681-685 [PMID: 24285337 DOI: 10.1097/01.TP.0000437790.26255.5d]

18 **Montenovo M**, Vaidya S, Bakthavatsalam R, Halldorson J. Pseudoaneurysm after combined kidney/pancreas transplantation presenting with sentinel bleeding: a case report and review. *Ann Transplant* 2014; **19**: 317-319 [PMID: 24995594 DOI: 10.12659/AOT.890356]

19 **Moya-Herraiz A**, Muñoz-Bellvis L, Ferrer-Fábrega J, Manrique Municio A, Pérez-Daga JA, Muñoz-Casares C, Alarcó-Hernández A, Gómez-Gutiérrez M, Casanova-Rituerto D, Sanchez-Bueno F, Jimenez-Romero C, Fernández-Cruz Pérez L. Cooperative Study of the Spanish Pancreas Transplant Group (GETP): Surgical Complications. *Cir Esp* 2015; **93**: 300-306 [PMID: 25638511 DOI: 10.1016/j.ciresp.2014.12.006]

20 **Leone John P**, Christensen K, Bhargava R, Hunter DW, Troppmann C, Lazaron V, Dunn DL, Paraskevas S, Coad JE, and Gruessner RWG. "Postoperative management." In: Transplantation of the Pancreas. New York: Springer, 2004: 179-266 [DOI: 10.1007/978-1-4757-4371-5_9]

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