2. Pancreas and islet cell transplantation

2.1. Induction therapy

2.1.1 Pancreas transplant induction therapy

Amorese G, et al (2020). Induction and immunosuppressive management of pancreas transplant recipients. Curr Pharm Des. 26(28):3425-3439. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32351176/

- Literature review of current practice and developments in immunosuppressive regimens in pancreas transplantation. Induction used in ~90% with Tcell depleting induction ~90% of the time. Initial enthusiasm with steroid-free maintenance regimens however now mostly still steroid-maintenance along with tac/mmf. MTOri introduced later ~10% of the time, mostly due to CNI side effects.

Bosmuller C, et al (2019). Good results with individually adapted long-term immunosuppression following alemtuzumab versus ATG induction therapy in combined kidney-pancreas transplantation: a single-center report. Ann Transplant. 24:52-56. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30679414/

- Retrospective analysis of long-term results of a randomized controlled trial comparing alemtuzumab induction plus tacrolimus monotherapy to antithymocyte globulin induction plus tacrolimus, mycophenolate mofetil, and steroids followed by individualized long-term immunosuppression in 30 SPK patients between 2006 and 2010. 5- year and 9-year pancreas graft, renal graft, and patient survival were similar between groups.

Fridell JA, et al (2018). Steroid-free three-drug maintenance regimen for pancreas transplant alone: Comparison of induction with rabbit antithymocyte globulin +/- rituximab. Am J Transplant. 18(12):3000-3006. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29738100

- Retrospective study of 166 PTX who received induction with rabbit antithymocyte globulin +/- rituximab and maintenance therapy with tacrolimus, sirolimus, and mycophenolate mofetil.

Li J, et al (2018). Dual antibody induction and de novo use of everolimus enable low dose tacrolimus with early corticosteroid withdrawal in simultaneous pancreas-kidney transplantation. Transpl Immunol. 50:26-33. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29885442

- Cohort study in which 25 SPK recipients received 2 doses of basiliximab and intraoperative thymoglobulin. Thymoglobulin could be redosed within the first week to maintain absolute lymphocyte below 500/µL. All patients were steroid free by POD7. Maintenance immunosuppression included tacrolimus and everolimus. The BPAR within the first 12 months was 13%. During a median follow-up of 58 months, new-onset diabetes mellitus and renal function deterioration were rare events. No cytomegalovirus activation was encountered. The patients, pancreas and kidney graft survival at 1-year and 5-year was 100% and 94.4%, 95.8% and 95.8%, 100% and 100% respectively.

Bank JR, et al (2016). Alemtuzumab induction and delayed acute rejection in steroid free simultaneous pancreas-kidney transplant recipients. Transplant Direct. 3(1):1-9. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28349124

- Cohort study assessing incidence and time to acute rejection episodes (AREs) in 73 SPK transplants receiving either alemtuzumab + steroid free maintenance (tacrolimus + mycophenolate mofetil) or antithymocyte globulin + triple therapy maintenance (tacrolimus + mycophenolate + steroid). Overall number of AREs at 3 years was significantly lower with alemtuzumab versus ATG induction (26.0% vs 43.5%; adjusted hazard ratio, 0.38; P = 0.029). Most AREs (94.6%) with ATG occurred within the first month, whereas 84.2% of AREs with alemtuzumab occurred beyond 3 months.

Fernandez-Burgos I, et al (2015). Induction therapy in simultaneous pancreas-kidney transplantation: thymoglobulin versus basiliximab. Transplant Proc. 47(1): 120-2. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25645787.

- Retrospective study of thymoglobulin vs basiliximab induction in SPK transplant recipients between February 2000 and August 2013 at a single center. Thymoglobulin group had less overall cellular rejection (P=0.045) and improved, though not statistically significant, patient survival at 1, 3, and 5 years follow-up. No difference in pancreas graft survival at any point. Major complications and median length of hospital stay were higher in the basiliximab group.

Stratta RJ, et al (2014). 5-year results of a prospective, randomized, single-center study of alemtuzumab compared with rabbit antithymocyte globulin induction in simultaneous kidney-pancreas transplantation. Transplant Proc. 46(6):1928-31. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25131073.

- Prospective study comparing outcomes in 46 SPK transplant recipients receiving induction with either alemtuzumab or rabbit antithymocyte globulin conducted from February 2005 to October 2008. There was no difference in patient or allograft survival as well as rates of acute rejection at 5 years follow-up between either groups. CMV infection rates were significantly lower utilizing alemtuzumab induction versus rabbit antithymocyte globulin.

Bazerbachi F, et al (2011). Thymoglobulin versus basiliximab induction therapy for simultaneous kidney pancreas transplantation: impact on rejection, graft function, and long-term outcome. Transplantation, 92(9):1039-43. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22002345.

- Retrospective study of thymoglobulin vs basiliximab induction in SPK transplant recipients between January 2001 and August 2008 at a single center. Thymoglobulin induction was associated with decreased rejection at 3 months and 1 year posttransplant. Long-term graft function and survival were not different between the two groups.

Uemura T, et al (2011). Single dose of alemtuzumab induction with steroid-free maintenance immunosuppression in pancreas transplantation. Transplantation, 92(6):678-85. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21841541.

- Retrospective, single-center study of patients who underwent pancreas transplantation (SPK, PAK, or PTA) and received alemtuzumab induction therapy. A single dose of alemtuzumab induction therapy demonstrated patient and graft survival results comparable to other induction agents over median follow-up of 25 months.

Farney AC, et al (2009). A randomized trial of alemtuzumab versus antithymocyte globulin induction in renal and pancreas transplantation. Transplantation, 88(6):810-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19920781.

- Prospective, randomized, single-center trial comparing alemtuzumab and thymoglobulin induction therapy in kidney and pancreas transplant recipients. Alemtuzumab was associated with less rates of rejection compared to thymoglobulin. Graft loss at 7 and 90 days were 4% and 5%, and 1-year patient and graft survival were 97% and 91%. Comparing induction with and without rituximab, there was no significant difference in 7- or 90-day graft loss, 1-year patient or graft survival, or in the rate of rejection or infection.

Magliocca JF, et al (2008). A comparison of alemtuzumab with basiliximab induction in simultaneous pancreas kidney transplantation. Am J Transplant. 8(8):1702-10. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18694474.

- Retrospective, single-center study of SPK patients using alemtuzumab induction compared with historical controls that received basiliximab. No difference observed in terms of survival, DGF, EBV/BKV infection, PTLD, or sepsis. Increase in CMV infection in the alemtuzumab-treated group (P=0.002) led to use of a single 30 mg dose of alemtuzumab instead of two doses. Long-term effects remained to be seen.

Zhang R, et al (2007). The long-term survival of simultaneous pancreas and kidney transplant with basiliximab induction therapy. Clin Transplant. 21(5):583-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17845631.

- Retrospective, single-center review of SPK patients who received basiliximab induction therapy from March 1998 to August 2005. Basiliximab induction with TAC, MFA, and steroid maintenance can provide good longterm patient and graft outcomes with low incidence of rejection and CMV.

Kaufman DB, Leventhal JR, Gallon LG, Parker MA (2006). Alemtuzumab induction and prednisone-free maintenance immunotherapy in simultaneous pancreas-kidney transplantation comparison with rabbit antithymocyte globulin induction- long-term results. Am J Transplant. 6(2):3319. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16426317.

- Retrospective, non-randomized, single-center study to evaluate alemtuzumab vs thymoglobulin induction with a prednisone free, tacrolimus/sirolimus based immunosuppression protocol. Long term graft and patient survival, infection and malignant complications and rejection rates did not differ between the groups.

2.1.2 Islet cell transplant induction therapy

Nordheim E, et al (2021). Patient selection for islet or solid organ pancreas transplantation: experiences from a multidisciplinary outpatient-clinic approach. Endocr Connect. 10(2):230-239. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33544090/.

- Retrospective chart review of pre-transplant evaluation, allocation, and 1-year clinical outcomes of patients with Type 1 diabetes undergoing beta-cell replacement therapy (either pancreas transplant alone (PTA) or islet cell transplant (ITX)) at a national transplant center in Norway.

Evaluation for transplant candidacy by a multidisciplinary team was associated with a significant reduction in referral of patients compared to prior evaluation by a single nephrologist (84% vs. 40%; -<0.005)

Tamburrini R, Odorico JS (2021). Pancreas transplant versus islet transplant versus insulin pump therapy: in which patients and when? Curr Opin Transplant. 26(2):176-183. Retrieved from: https://journals.lww.com/co-transplantation/Abstract/2021/04000/Pancreas_transplant_versus_islet_transplant_versus.12.aspx

- Review article of current practice, benefits, and challenges associated with insulin therapy, pancreas transplant, and islet cell transplant in the management of patients with diabetes mellitus

Bellin MD, et al (2012). Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. Am J Transplant. 12(6):1576-83. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22494609.

- Prospective, multi-center, open-label study of patients undergoing islet cell transplantation from 2002 to 2008. Patients received one of four possible induction regimens. Induction with ATG in combination with a TNF-α inhibitor (etanercept) had higher rates of insulin independence at 5 years comparable which was comparable to pancreas transplant.

Faradji RN, et al (2008). Long-term insulin independence and improvement in insulin secretion after supplemental islet infusion under exenatide and etanercept. Transplantation, 86(12):1658-65. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/19104401.

- Prospective in 9 islet transplants study examining the efficacy of a modified Edmonton protocol with the addition of exenatide and etanercept to induction with daclizumab compared to the standard Edmonton protocol group. All patients in the modified protocol group (n=5) had insulin independence at 18 months post islet cell transplantation compared to only 20% in the standard group (n=4).

2.2. Maintenance therapy

Kovac D, et al (2021). Immunosuppression considerations in simultaneous organ transplant. Pharmacother. 41(1):59-76. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33325558/

- Review article summarizing immunosuppression strategies for simultaneous solid organ transplantation recipients published between 1/1/2010 and 5/1/2020. Includes a focus on induction and maintenance immunosuppression practices in simultaneous pancreas kidney (SPK) transplantation and impact on patient survival.

Cantarovich D, et al (2020). Tacrolimus-versus sirolimus-based immunosuppression after simultaneous pancreas and kidney transplantation: 5-year results of a randomized trial. Am J Transplant. 20(6):1679-1690. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32022990/

- Single-center, open-label, prospective, randomized study in SPK recipients randomized to a tacrolimus or sirolimus based immunosuppressive regimen. Data from this study showed noninferiority of SRL compared to TAC when introduced at 3 months after SPK with regard to graft survival. Results do not favor SRL use as cornerstone therapy after SPK given high rates of discontinuation.

Girman P, et al (2020). Sirolimus vs mycophenolate mofetil (MMF) in primary combined pancreas and kidney transplantation. Results of a long-term prospective randomized study. Am J Transplant. 20(3):779-787. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31561278/

- Single-center, open-label randomized trial comparing pancreas graft survival in in SPK transplant recipients receiving sirolimus or MMF in combination with tacrolimus and early steroid withdrawal.

Data from this study demonstrate that sirolimus in combination with tacrolimus is an effective maintenance regimen in SPK transplant recipients.

Kaplan A, et al (2020). Long-Term Infectious and Noninfectious Outcomes of Monthly Alemtuzumab as a Calcineurin Inhibitor- and Steroid-Free Regimen for Pancreas Transplant Recipients. Can J Infect Dis Med Microbiol. 2020:8883183. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33101558/

- Long-term infectious and noninfectious outcomes of 179 pancreas transplant recipients treated with alemtuzumab induction and maintenance therapy (EAE (extended alemtuzumab exposure) to minimize CNI and/or steroids) vs. 159 pancreas transplant patients with standard induction and maintenance therapy.

Marcella-Neto R, de Sá JR, Melaragno CS, Gonzalez AM, Salzedas-Neto A, Linhares MM, Medina-Pestana JO, Rangel ÉB (2020). Late Conversion to Sirolimus or Everolimus After Pancreas Transplant. Transplant Proc. 52(5):1376-1379. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32213293/

- 490 SPK, 45 PAK pt. 13 switched to mtor-I from either CNI or MMF due to side effects (mostly CMV or GI intolerance) at ~11 months post-txp. ~13% discontinuation rate in the MTORi group (proteinuria, pharmacodermia), clinical complications included kidney and pancreas graft dysfunction; howeve,r low acute rejection rates. 20% graft loss over 15 years attributed to chronic allograft dysfunction.

Stock PG, et al (2020). Challenges of calcineurin inhibitor withdrawal following combined pancreas and kidney transplantation: Results of a prospective, randomized clinical trial. Am J Transplant. 20(6):1668-1678. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32039559/

- Multicenter, open-label, phase II, randomized study comparing belatacept-based immunosuppressive regimen to a CNI-based regimen in SPK recipients. Results of this study did not provide sufficient evidence to prevent pancreas rejection in SPK patients receiving belatacept while undergoing CNI withdrawal.

Torabi J, et al (2020). The use of LCP-Tacrolimus (Envarsus XR) in simultaneous pancreas and kidney (SPK) transplant recipients. Am J Surg. 219(4):583-586. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32122660/

- Single-center, retrospective study of SPK recipients between June 2014 and October 2018. Data from this study show that LCPT is a safe, effective method of administering tacrolimus in pancreas transplant patients.

Siskind EJ, et al (2019). Use of mammalian target of rapamycin inhibitors for pancreas transplant immunosuppression is associated with improved allograft survival and improved early patient survival. Pancreas. 48(5):644-651. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31091210/

- Data was analyzed from UNOS database for adult pancreas and SPK transplant recipients between 1987 and 2016. Data from this analysis showed improved allograft survival and early patient survival with the use of mTORi for immunosuppression following pancreas transplant

Benedini S, et al (2018). Insulin-mimetic effects of short-term rapamycin in type 1 diabetic patients prior to islet transplantation. Acta Diabetol. 55(7):715-722. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29654388/

- Multicenter, prospective study comparing rapamycin pre-treatment before islet transplant (n=13) to no rapamycin pre-treatment (n=28). Data from this study suggest that rapamycin pre-treatment before islet transplantation succeeds in reducing insulin requirements before and after transplantation.

Berney T, Andres A, Toso C, Majno P, Squifflet JP (2018). mTOR Inhibition and Clinical Transplantation: Pancreas and Islet. Transplantation, 102(2S Suppl 1):S30-S31. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28230643/

- Sirolimus was the cornerstone of islet cell txp maintenance at the turn of the century when it was used in 80% of regiments however this has now decreased to 50%. For pancreas txp, use of mtor-I has decreased from 20% to 10%. Decreased use of mtor-I likely due to side effects and lack of better outcomes however remains a valuable second-line agent.

Knight RJ, et al (2018). Conversion from tacrolimus-mycophenolate mofetil to tacrolimus-mTOR immunosuppression after kidney-pancreas transplantation reduced the incense of both BK and CMV viremia. Clin Transplant. 32(6):e13265. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29676018/

- Single-center, retrospective study of SPK recipients between December 2009 and June 2015 converted from TAC/MMF into TAC/mTOR immunosuppression. In this study, conversion from MMF to an mTOR inhibitor with a reduction in TAC dosing provided more effective prophylaxis against both CMV and BK viral replication than standard immunosuppression with TAC/MMF without compromising graft survival and acute rejection rates.

Jin J, et al (2017). Effect of empagliflozin on tacrolimus induced pancreas islet dysfunction and renal injury. Am J Transplant. 17(10):2601-2616. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28422431.

- Report of rat model evaluation of SGLT-2 inhibitor empagliflozin on tacrolimus induced diabetes mellitus. Data from this study show that empagliflozin improved tacrolimus induced hyperglycemia with probable impact on decrease of SGLT-2 expression. Additionally, plasma insulin level increased and islet size recovered.

Brennan DC, et al (2016). Long-term follow-up of the Edmonton Protocol of islet transplantation in the United States. Am J Transplant. 16(2):509-17. Retrieved from: https://www-ncbi-nlm-nih-gov/pubmed/26433206.

- Report of long term follow up evaluating efficacy and safety of islet transplantation in seven type 1 diabetic subjects from the United States enrolled in international Edmonton Protocol. Data from this report support safety of Edmonton Protocol in long-term evaluation even with low rate/duration of insulin independence.

Tekin Z, et al (2016). Outcomes of pancreatic islet allotransplantation using the Edmonton Protocol at the University of Chicago. Transplant Direct. 2(10):e105. eCollection 2016 Oct. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27795987.

- Report of long-term follow up of patients who underwent pancreatic islet cell transplantation under the Edmonton Protocol. Results from this report demonstrate durable long-term insulin-free diabetes control with islet transplant in patients with brittle diabetes.

Amodu Li, et al (2015). Steroid maintenance is associated with an increased risk of infections but has no effect on patient and graft survival in pancreas transplantation: a retrospective review of the UNOS database. Pancreatology, 15(5):554-562. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26330202.

- Report of an evaluation of UNOS database reviewing adult patients who received pancreas and kidney-pancreas transplants from January 1996 to March 2014 to evaluate the appropriateness of steroid maintenance. Data from this review demonstrates that maintenance steroid therapy may have no impact on patient or graft survival with utilization of thymoglobulin induction therapy. Additionally, steroid maintenance may be associated with higher incidence of post-op infections.

Qi M, et al (2014). Five-year follow-up of patients with type 1 diabetes transplanted with allogeneic islets: the UIC experience. Acta Diabetol. 51(5):833-43. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25034311.

- Report of a five-year, single-center, open label, prospective phase I/2 follow up outcomes in 10 islet cell transplants at the University of Illinois Hospital and Health Sciences Center. Data from this single center experience demonstrate long-term insulin independence with thymoglobulin induction in additional to Edmonton protocol.

Sageshima J, et al (2014). Everolimus with low-dose tacrolimus in simultaneous pancreas and kidney transplantation. Clin Transplant. 28(7):797-801. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24779669.

- Report of a retrospective analysis of 23 SPK recipients at a single center from November 2011 to March 2013 evaluating safety and efficacy of everolimus compared to mycophenolate sodium in SPK transplants. Data from this analysis demonstrates comparable short-term outcomes with everolimus and mycophenolate sodium in combination with FK/steroids and dual induction.

Bosmuller C, et al (2012). Tacrolimus monotherapy following alemtuzumab induction in combined kidney-pancreas transplantation: results of a prospective randomized trial. Ann Transplant. 17(4):45-51. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23274323.

- Report of single center experience with alemtuzumab induction and tacrolimus maintenance therapy compared to thymoglobulin induction with tacrolimus + mycophenolate + steroids maintenance in kidney-pancreas transplant patients. Data from this single center experience demonstrated comparable efficacy and safety of alemtuzumab induction and FK maintenance therapy compared to rabbit thymoglobulin induction with FK+ MMF+ steroids maintenance in kidney-pancreas transplant patients.

Ciancio G, et al (2012). 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. 12(12):3363-76. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22946986.

- Report of randomized, prospective, single-center trial of either mycophenolate mofetil or rapamycin in combination with tacrolimus for maintenance immunosuppression after simultaneous pancreas-kidney transplant. Results from this single center experience demonstrate that rapamycin combination with FK was better tolerated with more effective antirejection profile than MMF.

Peixoto EM, et al (2011). Effect of exenatide on gastric emptying and graft survival in islet allograft recipients. Transplant Proc. 43(9):3231-4. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22099764.

- Report of a prospective study in 10 patients examining long-term use (up to 4 years) of exenatide in islet transplantation to examine the effect on gastric emptying and graft survival. Data from this study demonstrate that exenatide treatment suppressed abnormal glucagon response, delayed average time to glucose peak, and prolonged graft survival. However, the more acute effects of exenatide use were not maintained once the medication was discontinued.

Knight RJ, et al (2010). Comparing an early corticosteroid/late calcineurin-free immunosuppression protocol to a sirolimus-, cyclosporine A-, and prednisone-based regimen for pancreas-kidney transplantation. Transplantation, 89(6):727-32. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20195219.

- Report of a nonrandomized, single-center, sequential study of low-immune responder SPK patients (PRA <50%) evaluating triple maintenance immunosuppression (n=20) or sirolimus maintenance with early steroid withdrawal followed by late CNI withdrawal (n=22). Data from this

study demonstrate that low-immune responder SPK patients achieved similar graft survivals at 2-years with prednisone/CNI free maintenance regimen. These patients also had an improved renal profile.

Malheiro J, et al (2009). Steroid withdrawal in simultaneous pancreas-kidney transplantation: a 7-year report. Transplant Proc. 41(3):909-12. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19376386.

- Report of a retrospective review of 77 SPK patients from May 2000 to December 2007 who received thymoglobulin induction therapy and tacrolimus and mycophenolate mofetil maintenance therapy with a late steroid withdrawal protocol. Results of this study reflect safety of steroid withdrawal without increase in immune related events.

Froud T, et al (2008). The use of exenatide in islet transplant recipients with chronic allograft dysfunction: safety, efficacy, and metabolic effects. Transplantation, 86(1):36-45. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/18622276.

- Report of a prospective study in 16 islet cell transplant recipients given exenatide for allograft dysfunction causing a new insulin requirement post-islet transplantation. Results of this study demonstrate that exenatide was well tolerated post-islet transplant with appropriate dose titration allowing for gradual and sustained positive outcomes on glycemic control.

Gallon LG, et al (2007). Long-term renal transplant function in recipient of simultaneous kidney and pancreas transplant maintained with two prednisone-free maintenance immunosuppressive combinations: tacrolimus/mycophenolate mofetil versus tacrolimus/sirolimus. Transplantation, 83(10):1324-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17519781.

- Report of a retrospective, single-center, sequential study of 59 SPK transplant patients evaluating impact of long-term renal allograft function of two steroid-free maintenance regimens with tacrolimus. Data from this single center study suggest similar outcomes and a numerically lower incidence of kidney graft survival with maintenance regimen of FK/sirolimus compared to FK/MMF.

Rajab A, et al (2007). Steroid-free maintenance immunosuppression with rapamune and low-dose neoral in pancreas transplant recipients. Transplantation. 84(9):1131-7. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17998868.

- Report of a retrospective, single-center review of new steroid free pancreas transplant protocol implementation. Data from this single center experience demonstrate excellent graft survival with significantly reduced acute rejection incidence via steroid-free maintenance therapy with CsA and rapamycin.

Vessal G, et al (2007). Early steroid withdrawal in solitary pancreas transplantation results in equivalent graft and patient survival compared with maintenance steroid therapy. Clin Transplant. 21(4):491-7. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17645708.

- Report of a retrospective, single-center evaluation of early steroid withdrawal in solitary pancreas transplants between January 2001 and December 2003. Data from this single center study demonstrate early steroid withdrawal in isolated pancreas transplant (either alone or after kidney transplant) can be achieved without increased rejection or graft loss rates during the first year.

Fridell JA, et al (2006). Steroid withdrawal for pancreas after kidney transplantation in recipients on maintenance prednisone immunosuppression. Transplantation, 82(3):389-92. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16906038.

- Report of a retrospective single-center review of pancreas after kidney transplants between June 2003 and January 2006 evaluating steroid withdrawal from patients taking prednisone for

previous renal transplant. Data from this single center review postulate safe withdrawal of steroids in PAK transplant recipients if thymoglobulin utilized for induction with FK and sirolimus maintenance.

Shapiro AM, et al (2006). International trial of the Edmonton protocol for islet transplantation. N Engl J Med. 355: 1318–1330. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17005949.

- Report of a single group, multicenter study of outcomes in islet cell transplantation utilizing Edmonton Protocol to explore the feasibility and reproducibility of islet transplantation. Data from this trial demonstrate that islet transplantation utilizing the Edmonton Protocol can restore endogenous insulin production and provide stability in blood glucose levels; however, insulin independence on average lasted 2 years posttransplant.

Gruessner RW, et al (2005). Calcineurin inhibitor- and steroid-free immunosuppression in pancreas-kidney and solitary pancreas transplantation. Transplantation, 79(9):1184-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15880067.

- Report of a prospective, nonrandomized, observational cohort study of 75 SPK and PTA patients who received alemtuzumab induction with mycophenolate induction and maintenance therapy compared to a historical group of 266 patients that received thymoglobulin induction and tacrolimus maintenance. Results of this study demonstrate alemtuzumab and MMF regimen associated with acceptable rejection rate with potential to eliminate undesired CNI and steroid related side effects; however, longer follow up is lacking.

Bechstein WO, et al (2004). Efficacy and safety of tacrolimus compared with cyclosporine microemulsion in primary simultaneous pancreas-kidney transplantation: 1-year results of a large multicenter trial. Transplantation, 77(8):1221-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15114089.

- Report of an open-label, multicenter study comparing efficacy and safety of tacrolimus with microemulsion cyclosporine in patients who received SPK transplantation. Biopsy proven kidney or pancreas acute rejection at one-year were lower with FK arm (27.2%) compared to microemulsion CsA (38.2%), p=0.09. Data from this study demonstrate support for FK therapy in patients undergoing SPK due to type 1 diabetes with end-stage renal disease.

Shapiro AM, et al (2000). Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 343:230-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/10911004.

- Introduction of Edmonton Protocol for islet cell transplantation. Observation from this registry data demonstrate that islet transplant in type 1 diabetic patients can lead to insulin independence with metabolic control in a steroid-free immunosuppression regimen.

Stegall MD, et al (1997). Mycophenolate mofetil decreases rejection in simultaneous pancreas-kidney transplantation when combined with tacrolimus or cyclosporine. Transplantation. 64(12):1695-700. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/9422404.

- Report of a single center, prospective, randomized study evaluating acute rejection rates and morbidity in SPK transplant recipients when mycophenolate mofetil was added to maintenance regimen. Data from this study show that MMF treatment significantly decreases incidence of biopsy proven acute rejection in SPK patient compared to AZA in historical group.

2.3 Desensitization therapy

Kykalos S, et al (2017). Successful simultaneous pancreas-kidney re-transplant in a highly human leukocyte antigen-sensitized patient. Transplantation Proceedings:49: 1652-1655. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28838458

- Single patient case report of a 45 year old female with a SPK in 2004 secondary to juvenile diabetes mellitus type I. Transplantation was complicated by rejection and loss of organ function for both organs in 2009. Highly sensitized (PRA >85%). Desensitization Protocol: Rituximab 375 mg/m^2 (max 650 mg) x1 dose, plasmapheresis + IVIG x5 doses every 14 days.

Mattiazzi AD, et al (2014). Highly sensitized patients: Miami transplant institute experience. Clinical Transplant. 171-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26281142.

- Studied allograft failure in 45 highly sensitized patients (RTX and SPK). The cumulative proportion of patients who remain free of death or allograft failure was significantly higher in the Rituximab (87%) versus the Control group (60%) (p = 0.047).

Heilman RL, et al (2009). Outcomes of simultaneous kidney-pancreas transplantation with positive crossmatch. Transplantation Proceedings, 41: 303-306. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19249540.

- Studied 72 consecutive simultaneous pancreas kidney transplant (SPKT) recipients
- Study group: 14 patients with positive pretransplant cross-matches (positive CDC- B cell and/or positive flow T or B cross-match). Induction with low dose intravenous immunoglobulin (IVIg), rabbit antithymocyte globulin (rATG; total dose 6 mg/kg), or alemtuzumab (30 mg single dose) and maintenance with tacrolimus, mycophenolate mofetil (MMF), and corticosteroids.
- Control group: 58 SPKT recipients with a negative crossmatch . Induction with rabbit antithymocyte globulin (rATG; total dose 6 mg/kg), or alemtuzumab (30 mg single dose) and maintenance with tacrolimus, mycophenolate mofetil (MMF), and steroid avoidance.

2.4. Diagnosis and management of rejection

Barros N, et al (2021). Rabbit anti-thymocyte globulin administration to treat rejection in simultaneous pancreas and kidney transplant recipients with recent COVID-19 infection. Clin Transplant.:e14149. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33179350/

- Use of thymoglobulin for steroid-resistant acute rejection in 2 SPK patients who had recovered from COVID-19 but still with viral shedding
    - Patient #1 had mild COVID-19 without reduction in IMS, rejection diagnosed based on lipase elevation and imaging, which did not improve after steroids. Did improve after thymoglublin.
    - Patient #2 with asymptomatic COVID-19, elevated Scr and new DSA. ACR plus chronic active AMR. SCr did not respond to PP/IVIG/rituximab/thymoglobulin, but he did not become symptomatic from COVID-19.

Ladowski JM, et al (2021). Eplet mismatch scores and de novo donor-specific antibody development in simultaneous pancreas-kidney transplantation. Hum Immunol. 82(3):139-146. doi: 10.1016/j.humimm.2020.12.009. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33390268/.

- Comparison of HLA incompatibility scores of various algorithms to predict de novo DSA development and impact on graft survival in simultaneous pancreas kidney transplant recipients
- Female sex and race were found to be significantly associated with development of de novo DSA post-transplant. De novo DSA development was associated with AMR and worse graft outcomes.

Aziz F, et al (2020). Alloimmunity in pancreas transplantation. Curr Opin Organ Transplant. 25(4):322-328. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32692039/

- Pre-transplant and de-novo DSA both associated with increased risk for AMR. Pancreas allograft biopsy essential for differentiating between ACR and AMR and guiding therapy for both PTA and also SPK and biopsy findings have found to be discordant. Treatment of rejection can prolong graft survival.

Aziz F, et al (2019). How should pancreas transplant rejection be treated? Transplantation, 2019;103(9):1928-1934. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31233481/

- Single-center retrospective review of 158 pancreas recipients treated for first episode of BPAR comparing response rate and long-term outcomes with steroids alone versus steroids plus ATG.
- 65 patients were treated with steroids alone; 83% of patients with grade I BPAR, 60% with grade II, and 33% with grade III responded to steroids alone. 93 patients were treated with steroids plus ATG; response rates were 69% in grade I, 76% in grade II, and 73% in grade III. Response rates and graft survival were not different with grade I rejection treated with either option, however, response rates and graft survival were significantly better with grade III rejection treated with the addition of ATG, and graft survival rates were significantly better with grade II rejection treated with the addition of ATG.

Loupy A, et al (2017). The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology. Am J Transplant. 17(1):28-41. Retrieved from: http://onlinelibrary.wiley.com/doi/10.1111/ajt.14107/full.

- Updated Banff pancreas allograft rejection grading schema located in table 7 (page 3839)

Redfield RR, Rickels MR, Naji A, Odorico JS (2016). Pancreas Transplantation in the Modern Era. Gastroenterol Clin North Am. 45(1):145-66. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26895686

- Review of current indications, patient selection, surgical considerations, complications, and outcomes in the modern era of pancreas transplantation.
- Includes rejection diagnosis and treatment algorithm (pages 156-160, table 6).

Salahuddin S, Astor B, Parajuli S, Djamali A, Odorico J, Mandelbrot D (2016). Outcomes with Steroids Alone for Biopsy-Proven Pancreas Transplant Rejection. [abstract]. Am J Transplant. 16 (suppl 3). Retrieved from: https://atcmeetingabstracts.com/abstract/outcomes-with-steroidsalone-for-biopsy-proven-pancreas-transplant-rejection/

- Retrospective review of 42 pancreas transplant recipients from January 1997 to December 2013 who had biopsy proven rejection and were treated with steroid pulse alone.
- Patients with grade 1 pancreas transplant rejection can be treated with steroids alone (62% responded to treatment), where grade 2 and 3 rejection rarely responded to steroids alone (14% responded) and was associated with higher graft failure rates.

Redfield RR, et al (2015). Diagnosis and Treatment of Pancreas Rejection. Curr Transplant Rep. 2015;2(2):169-175. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26000231.

- Review of the diagnosis and treatment of pancreas rejection. Rejection treatment algorithm from the University of Wisconsin.

De Kort H, et al (2014). Diagnosis of early pancreas graft failure via antibody mediated rejection: single-center experience with 256 pancreas transplantations. Am J Transplant. 14(4):936-42. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24712331

- Retrospective review of 256 SKP between 1985-2010 at one center. A total of 33 SPKs lost their pancreas graft <1 year after transplant. AMR was diagnosed in 7 cases, 8 cases were suspicious for AMR and 18 cases were not due to AMR. All patients with acute AMR of the pancreas lost their renal grafts <1 year after transplant.

- Histopathological analysis of early pancreas graft loss is advisable to rule out the possibility of AMR, particularly because a diagnosis of acute AMR has important consequences for renal graft outcomes.

Dong M, et al (2013). Acute pancreas allograft rejection is associated with increased risk of graft failure in pancreas transplantation. Am J Transplant. 13(4):10191025. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23432918.

- Retrospective review of 227 consecutive pancreas transplants performed at one center from 1998 to 2009. Treatment of rejection included corticosteroid boluses along with either OKT3 (5 mg/day for 7- 10 days) or ATG (1.5 mg/kg/day for 5-10 days).
- Incidence of partial or complete loss was low due to treatment of acute rejection, however, acute rejection, especially within the first 3 months, was associated with an increased risk of long-term complete loss. Acute rejection within the first year was associated with an increased risk of at least partial loss.

Drachenberg CB, et al (2011). Guidelines for the diagnosis of antibody mediated rejection in pancreas allografts-updated Banff grading schema. Am J Transplant. 11(9):1792-802. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21812920

- Comprehensive guidelines for the diagnosis of AMR, best identified by a combination of serological and immunohistopathological findings consisting of identification of circulating donor-specific antibodies, and histopathological data
- Acute AMR is diagnosed conclusively if these three elements are present, whereas a diagnosis of suspicious for AMR is rendered if only two elements are identified. The identification of only one diagnostic element is not sufficient for the diagnosis of AMR but should prompt heightened clinical vigilance. AMR and ACMR may coexist, and should be recognized and graded independently.

2.5. Graft failure/retransplantation

Shingde, R, et al (2020). Relative survival and quality of life benefits of pancreas–kidney transplantation, deceased kidney transplantation and dialysis in type 1 diabetes mellitus—a probabilistic simulation model. Transpl Int, 33: 1393-1404. Retrieved from: https://onlinelibrary-wiley-com.proxy.cc.uic.edu/doi/10.1111/tri.13679.

- Australian and New Zealand registry data from 2006-2016 used to build a model to compare survival between SPK and DDRT with dialysis in terms of life years saved and quality-adjusted life years.
- SPK best treatment for those under age 50 with ESRD and type 1 DM. For those over age 50 and ineligible for SPK, DDRT offers survival benefit over dialysis.

Descourouez JL, et al (2020). Alemtuzumab induction for retransplantation after primary transplant with alemtuzumab induction. Clin Nephrol. 93(2):77-84. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31670651/.

- Retrospective, single-center study of patients undergoing retransplantation (kidney or pancreas) receiving induction with alemtuzumab or rabbit antithymocyte-globulin from January 2001 and December 2016. Both groups received alemtuzumab induction for their primary transplant.
- There was no difference in 1 year rejection rates but use of alemtuzumab induction for retransplantation was associated with a significantly higher incidence of fungal infections compared to rabbit antithymocyte-globulin.

Parajuli S, et al (2019). Pancreas retransplant after pancreas graft failure in simultaneous pancreas-kidney transplants is associated with better kidney graft survival. Transplant Direct.5(8):e473. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31576369/.

- Single-center cohort study of SPK recipients transplanted between 01/01/2000 and 12/31/2016 who experienced pancreas graft failure and retained kidney graft function. Patients were divided into groups that underwent pancreas retransplant and those who didn't.
- At last follow-up, 60% of the repeat pancreas graft has failed, with a mean graft survival among failed pancreas grafts of 2.6 years. Uncensored and death censored kidney graft failure was significantly lower in the retransplant group (44% vs. 67% and 24% vs. 67%, respectively).

Gasteiger S, et al (2018). Outcomes of pancreas retransplantion in patients with pancreas graft failure. Br J Surg.105(13):1816-1824. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30007018.

- Report of a retrospective observational study of pancreas retransplant (PRT) at a single center between 1997 and 2013.
- A total of 52 patients were identified as PRTs and median follow up was 65 months. Graft survival at 1 year and 5 years were 79% and 69% respectively, with patient survival rates of 96% and 89%. Though not statistically significant, 5 year graft survival was better after SPK retransplantion than PRT alone: 80% vs 63%, p=0.266.
- Results of this single center experience demonstrate PRT as an option for patients with primary pancreas transplant failure.

Gerber PA, et al (2018). Islet transplantation as safe and efficacious method to restore glycemic control and to avoid severe hypoglycemia after donor organ failure in pancreas transplantation. Clin Transplant. 32(1). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29140547.

- Report of single center experience assessing safety and efficacy of islet transplant after initial pancreas transplant with subsequent organ failure.
- Ten patients received islet transplant after pancreas organ failure and were followed for 51 months. Primary end point of hemoglobin A1c < 7% and freedom from severe hypoglycemia was achieved by 9/10 IAP, 3/3 PRT, and 0/7 control group. Insulin requirement decreased by 50% in IAP arm.
- Results from this single center experience support IAP after deceased donor pancreas graft failure as an option to improve glycemic control and reduce hypoglycemia events.

Perosa M, et al (2018). Outcomes after pancreas retransplantation: is the juice worth the squeeze? Curr Opin Organ Transplant. 23(4):461-466. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29979264.

- Review of current literature outlining outcomes of pancreas retransplantation as compared to primary pancreas transplant.
- Overall, a lower graft survival of PRTs is reported compared to primary pancreas transplantations. This finding could be due to differences in transplant category: primary pancreas transplantations are predominantly SPKs, which are known to have superior graft survival outcomes over solitary pancreas transplantations.

Andres A, et al (2015). Islet-after-failed-pancreas and pancreas-after-failed islet transplantation: Two complementary rescue strategies to control diabetes. Islets, 7(6):e1126036. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26854597.

- Report of single-center outcomes associated with pancreas transplant after failed islet transplant (n=2), and islet transplant after failed pancreas transplant (n=3).
- Data from this single center experience demonstrate both strategies to be feasible, however more robust data is warranted. PAI outcomes may be offset due to duration of waitlist time secondary to sensitized patient status.

Seal J, et al (2015). Outcomes of pancreas retransplantation after simultaneous kidney-pancreas transplantation are comparable to pancreas after kidney transplantation alone. Transplantation 99(3):623-8. Retrieved from: https://www-ncbi-nlm-nihgov/pubmed/25148379.

- Report of retrospective analysis evaluating short- and long-term outcomes for recipients of pancreas retransplant after primary pancreas after kidney transplantation.
- Pancreas graft survival similar between arms: PAK 88.2% vs PRT 100% at 1 year and PAK 85.1% vs PRT 85.1% at 3 year. At three years, both groups had comparable hemoglobin A1c, serum creatinine, and oral glucose tolerance tests. Results of this analysis demonstrate pancreas retransplantation as a safe and efficacious option as it was associated with similar postoperative complication risks and similar graft survival compared to primary PAK.

Siskind E, et al (2015). Pancreatic retransplantation is associated with poor allograft survival: an update of the United Network for Organ Sharing database. Pancreas, 44(5):769-72. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25931257.

- Report evaluating the outcomes of pancreas retransplant compared to primary pancreas transplant based on the data from the United Network for Organ Sharing database.
- Analysis of patient survival was superior for PRT arm ($p<0.0001$) while graft survival was superior in primary transplant arm ($p<0.0001$).
- Results from this analysis demonstrate a lower graft survival than previous studies, partially due to predominance of PAT versus SPK. Further studies are needed to determine true impact of PRT and identify specific patients who would benefit most.

Buron F, et al (2013). Pancreas retransplantation: a second chance for diabetic patients? Transplantation, 27;95(2):347-52. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23222920.

- Study aiming to evaluate pancreas retransplantation outcomes in type 1 diabetic patients with end stage renal disease who have lost their primary graft.
- Pancreas retransplanted patient graft survival was similar to primary graft survival of the whole population (71% vs. 79% at 1 year and 59% vs. 69% at 5 years; P=0.5075) and statistically better than first pancreas survival (71% vs. 29% at 1 year and 59% vs. 7% at 5 years; P=0.0008) regardless of cause of graft loss.
- Results of this report demonstrate pancreas retransplantation as a safe procedure with acceptable graft survival that should be proposed to diabetic patients who have lost their primary graft.

LaMattina JC, Sollinger HW, Becker YT, Mezrich JD, Pirsch JD, Odorico JS (2012). Simultaneous pancreas and kidney (SPK) retransplantation in prior SPK recipients. Clin Transplant. 26(3):495-501. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22032238.

- Retrospective review summarizing outcomes of repeat SPK in prior SPK recipients (n = 9) from a cohort of over 1200 SPK recipients.
- Median time to retransplant was 7.8 years. Retransplant pancreatic allograft survival was 78% at one year and 67% at two years.
- Data from this review support acceptable survival of repeat SPK allografts despite increased technical and immunologic demands of retransplantation. As 89% of patients underwent transplant nephrectomy and 78% underwent transplant pancreatectomy, a graftectomy prior to or at the time of retransplantation may be necessary.

2.6. Diabetes secondary to chronic pancreatitis or cystic fibrosis without pancreatectomy

Onady GM, Stolfi A (2020). Drug treatments for managing cystic fibrosis-related diabetes. Cochrane Database Syst Rev. 10:CD004730. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33075159/

- Updated systematic review determining the efficacy of insulin and oral agents for the management of diabetes in cystic fibrosis patients
- Outcomes evaluated include blood sugar control, pulmonary function, nutritional status, microvascular and macrovascular disease complications, complications, and mortality
- No conclusive evidence for superiority of one agent over another in controlling hyperglycemia or clinical outcomes associated with cystic fibrosis related diabetes

Ode KL, et al (2019). Cystic fibrosis related diabetes: medical management. J Cyst Fibros. 18(2):S10-S18. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31679720/

- Review and discussion of medical treatment options for patients with cystic fibrosis related diabetes

Ballman M, et al (2018). Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomized trial. The Lancet Diabetes & Endocrinology, 6(2): 114-121. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29199116

- Multicenter, open-label, randomized trial of 75 patients comparing insulin with repaglinide therapy for patients with newly diagnosed cystic fibrosis-related diabetes
- Results of the study showed no significant difference in the change in Hemoglobin-A1c, blood glucose concentration, FEV1, or FVC at 12 months or 24 months.

Kayani K, Mohammed R, Mohiaddin H (2018). Cystic-fibrosis related diabetes. Front Endocrinol. 9: 1-11. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29515516

- Review and discussion of the pathophysiology, complications, diagnosis, and management of cystic-fibrosis related diabetes mellitus.

Moran A, et al (2018). ISPAD clinical practice consensus guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes, 19(27):64-74. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30094886/

- Updated clinical guidelines for the management of cystic fibrosis related diabetes mellitus

Wynne K, Devereaux B, Dornhorst A (2018). Diabetes of the exocrine pancreas. Journal of Gastroenterology and Hepatology, 34(2):346-354. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30151918

- Review and discussion of the related etiologies, pathophysiology, screening, diagnosis, and treatment for diabetes of the exocrine pancreas

Yoon, C (2017). Evolving mechanistic views and emerging therapeutic strategies for cystic fibrosis related diabetes. Journal of the Endocrine Society, 1(11):1386-1400. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29264462

- Review and discussion of the pathophysiology, risk factors, and management of cystic fibrosis-related diabetes.

Ewald N, Hardt PD (2013). Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. World J Gastroenterol. 19(42):7276-81. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24259958.

- Review and discussion of the prevalence, diagnosis, and treatment of diabetes in chronic pancreatitis

Rickels MR, et al (2013). Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. Pancreatology, 13(4):336-42. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23890130

- Working group recommendations and review of the medical problems, diagnostic methods and treatment options for chronic pancreatitis-associated diabetes from a consensus meeting in 2012

Lek N, Acerini CL (2010). Cystic fibrosis related diabetes mellitus - diagnostic and management challenges. Curr Diabetes Rev. 6(1):9-16. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20034372.

- Review and discussion of the diagnosis and treatment of cystic fibrosis related to diabetes mellitus.

Mohan K, et al (2008). Long-Term Effect of Insulin Treatment in cystic fibrosis-related diabetes. Respiration, 76: 181-186. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17960051

- Retrospective, single-center, longitudinal cohort study of 42 patients with cystic fibrosis-related diabetes to determine the long-term impact (3 years) of insulin treatment on patients with cystic fibrosis-related diabetes
- Results showed significant improvement in FEV1, FVC and BMI at one year; however, the effect was only sustained at three years for BMI. FEV1 and FVC were not significantly different at 2 and 3 years after insulin initiation.

2.7. Pancreatectomy prior to pancreas transplant and/or islet autotransplant

Harindhanavudhi T, et al (2020). Body composition is associated with islet function after pancreatectomy and islet autotransplant for pancreatitis. J Clin Endocrinol Metab. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33124670/

- Single center retrospective review of 88 patients undergoing total pancreatectomy with islet autotransplantation (TPIAT) and the impact of pre-surgical body composition on islet function and sensitivity. Half of these chronic pancreatitis patients were overweight/obese; underweight was uncommon. Preoperative body weight and composition were associated with islet function but not insulin independence after TPIAT.

Balzano G, et al (2019). Diabetes-free survival after extended distal pancreatectomy and islet auto transplantation for benign or borderline/malignant lesions of the pancreas. Am J Transplant. 19(3):920-928. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30549450/

- Single center retrospective review of 25 patients that underwent left extended pancreatectomy (>60%) and islet autotransplant for a neoplasm located in the pancreatic neck or proximal body.
- There were no deaths and low morbidity. Patient and insulin-independent survival rates at 4 years were 100% and 96%, respectively. Glucose homeostasis remained within a nondiabetic range at all times for 19 (73%) of 25 patients. Patients undergoing islet autotransplant had a longer diabetes-free survival than did patients without islet autotransplant.
- In conclusion, islet autotransplant after extended pancreatic resection for neoplasms is a safe and successful procedure for preventing diabetes

Bellin MD, et al (2019). How durable is pancreatectomy and intraportal islet cell transplantation for treatment of chronic pancreatitis? J Am Coll Surg. 228(4):329-339. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30630085/

- Single center observational study of 742 patients who underwent a total pancreatectomy and intraportal islet cell autotransplant (TPIAT), 215 who have 10 year follow-up data, to determine long-term durability TPIAT

- 10-year actuarial survival rate was 72% with BMI >30 kg/m2 predicting 10-year mortality. Patient relief rates were 82% at 10 years and 90% at 15 years. 10-year insulin independence rate was 20% and partial graft function rate 32%. Dual procedure produced durable pain relief and sustained islet graft function, even post 10 years postoperatively.

Cerise A, Nagaraju S, Powelson JA, Lutz A, Fridell JA (2019). Pancreas transplantation following total pancreatectomy for chronic pancreatitis. Clin Transplant. 33(12):e13731. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31627258/

- Single center retrospective review of 8 patients that underwent total pancreatectomy and pancreas transplant between 6/1/2005 and 7/1/2006.
- Patient survival rate at 1 and 3 years was 88% with death-censored graft survival of 100% and 86%, respectively. 75% remained insulin-free until their time of death, loss of follow-up or present day with 75% of these patients maintaining exocrine function without pancreatic enzyme supplementation.

Colling KP, et al (2019). Total pancreatectomy with intra-portal islet autotransplantation as a treatment of chronic pancreatitis in patients with CFTR mutations. Pancreas. 47(2):238-244. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29206667.

- Single center outcomes comparison of total pancreatectomy with islet autotransplantation in patients with CFTR mutation associated chronic pancreatitis to those without CFTR mutation.
- At 1 year, 40% of CFTR homozygotes, 22% of CFTR heterozygotes, and 35% of control patients were insulin independent.
- Data from this single center experience convey similar outcomes for CFTR patients compared to those with chronic pancreatitis from other etiologies.

Kotagal M, et al (2019). In-hospital and 90-day outcomes after total pancreatectomy with islet autotransplantation for pediatric chronic and acute recurrent pancreatitis. Am J Transplant. 9(4):1187-1194. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30372594/

- Single-center retrospective review of the outcomes of 20 pediatric patients who underwent TPIAT.
- Mean age 13, 95% had chronic pancreatitis and 1 had acute recurrent pancreatitis alone. 90 days postoperatively vs. preoperatively there were significantly fewer patients receiving parenteral nutrition (0% vs 25%) and opioids (45% and 75%). Short Form 36-Item Health Survey scores also significantly improved. Insulin requirement decreased from 0.5 u/kg/d to 0.4 u/kg/d between discharge and 90 days. TPIAT is an effective option when debilitating disease persists despite maximal medical and endoscopic therapy.

Nijhoff MF, Dubbeld J, van Erkel AR, van der Boog PJM, Rabelink TJ, Engelse MA, de Koning EJP (2018). Islet alloautotransplantation: Allogeneic pancreas transplantation followed by transplant pancreatectomy and islet transplantation. Am J Transplant. 18(4):1016-1019. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29160954/.

- Case report of islet transplantation utilizing islet cells of the pancreas allograft which needed to be explanted due to bleed. 3 month outcomes show glycemic control, with some use of basal insulin.

Gruessner RW, et al (2018). Pancreas allotransplants in patients with a previous total pancreatectomy for chronic pancreatitis. J Am Coll Surg. 206(3):458-65. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18308216.

- Report of a single center experience of pancreas allotransplants with a previous total pancreatectomy for chronic pancreatitis.

- Pancreas graft survival at 1 and 3 years for CSA were 67% and 50%, for tacrolimus 73% and 51%, and CNI-free at 1 year was 40% (p=0.13).
- Data from this series of pancreas allotransplants showed graft survival rates of more than 70% with a tacrolimus-based immunosuppression regimen. Additionally, pancreas transplant demonstrated success in treating both endocrine and exocrine insufficiency.

Skube ME, Mills PD, Hodges JS, Beilman GJ, Bellin MD (2018). Islet graft function is preserved after pregnancy in patients with previous total pancreatectomy with islet autotransplant. Pancreas, 47(9):e64-e65. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30199492/

- Single-center retrospective review of women who had previously undergone TPIAT and subsequently completed pregnancies.
- 5 patients completed 7 total pregnancies with median time to conception of 21 months. 80% had increased exogenous insulin requirements; however compared to controls, no significant HbA1c, insulin use, or graft function differences were found at time of last follow-up. Long-term graft function was comparable between patients with a pregnancy after TPIAT and their matched controls, supporting the conclusion that pregnancy did not have a negative impact on graft function in women with a history of TPIAT.

Sutherland DE, et al (2012). Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg. 214(4):409-24; discussion 424-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22397977.

- Report of a more than 30-year single center series of 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet autotransplant.
- Patient survival at 1 and 5 years was 96% and 98% in adults, 89% and 98% in children.
- Data from this series support that total pancreatectomy and islet autotransplant can improve quality of life in refractory chronic pancreatitis. Additionally, islet autotransplant preserves islet function in most patients with insulin independence in 25% of adults.

Walsh RM, et al (2012). Improved quality of life following total pancreatectomy and autoislet transplantation for chronic pancreatitis. J Gastrointest Surg. 16(8):146977. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22673773.

- Single center experience for impact of total pancreatectomy with islet autotransplant for treatment of chronic pancreatitis on quality of life.
- Pain disability index improved from 79% preoperatively to 90% postoperatively (p=0.002). Up to 60% and 70% demonstrated improvement in depression and anxiety respectively (p=0.033).
- Data from this report demonstrate improvement in pain and quality of life in patients with chronic pancreatitis who underwent total pancreatectomy with islet autotransplant. Of note, greatest improvement was seen in patients without prior pancreatic surgery, younger aged, and higher level of preoperative pain.

Webb MA, et al (2008). Islet auto transplantation following total pancreatectomy: a long-term assessment of graft function. Pancreas, 37(3):282-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/18815550.

- Report of a single center series of 46 patients having undergone simultaneous total pancreatectomy with immediate islet autotransplant.
- At 10 years of follow up, 12 patients had shown periods of insulin dependence for a median of 16.5 months and 5 patients remained insulin dependent. All of the patients were c-peptide positive at most recent assessment with high fasting and stimulated c-peptide values during follow up: average of 1.44 ng/mL and 2.86 ng/mL respectively.
- Data from this series demonstrate that though there is a notable decline in islet function after autotransplant, evidence of long-term insulin secretion exists

Gruessner RW, et al (2004). Transplant options for patients undergoing total pancreatectomy for chronic pancreatitis. J Am Coll Surg. 198(4):559-67; discussion 568-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15051008.

- Report of a single center experience with islet autotransplants at the time of, or with pancreas allotransplants after total pancreatectomy.
- Transplant related mortality at 1 year and 3 years was not impacted by pancreas allotransplant after total pancreatectomy. Pancreas graft survival at 1 year was 77% with tacrolimus-based immunosuppression compared to 67% with cyclosporine.
- Data from this center supports pancreas allotransplant without transplant related mortality with tacrolimus-based immunosuppression.

2.8. Exocrine drainage in pancreas transplant

Goussous N, et al (2021). Is prophylactic drainage after pancreas transplant associated with reduced reoperation rate? Exp Clin Transplant. 19(1):64-71. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33272163/.

- Single-center retrospective review comparing post-operative complications and infections in 83 pancreas transplant recipients with intra-operative prophylactic drain placement vs. no drain placement
- Enteric drainage was utilized in all grafts and 30/83 (36%) of patients had at least one prophylactic drain placed. Prophylactic abdominal drain placement following pancreas transplant was associated with a lower incidence of need for reoperation for peripancreatic infections, but no difference in peripancreatic infections or graft survival

Raid SM, et al (2020). Enteric conversion of bladder-drained pancreas as a predictor of outcomes in almost 600 recipients at a single center. Transplant Direct. 6(5):e550. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32548244/

- Retrospective, single center study of 593 pancreas transplant patients with bladder-drained pancreata. Patients who underwent enteric conversion were compared to those who did not.
- Enteric conversion was associated with an increased risk of acute rejection but was not associated with a higher rate of graft loss or mortality.

Adler JT, et al (2019). Enteric conversion after bladder-drained pancreas transplantation is not associated with worse allograft survival. Am J Transplant. 19(9): 2543-2549. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30838785/

- Retrospective, single center study of first-time SPK transplants with bladder drainage performed between 1985 and 2000. Patients who underwent enteric conversion were compared to those who did not.
- Enteric conversion was not associated with a difference in pancreas or kidney graft survival.

Byrne M, et al (2019). Bladder-Drained Pancreas Transplantation: Urothelial Innate Defenses and Urinary Tract Infection Susceptibility. J Surg Res. 235:288-297. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30691808/

- Retrospective review of bladder-drained (BD) and enteric-drained (ED) pancreas transplant patients for UTI and urine was analyzed for pH and host defense proteins/peptides (HDPs) which increase susceptibility to UTIs.
- In-vitro analysis showed decreased growth of Ecoli in an alkaline pH and increased growth with the addition of pancreatin (pancreatic digestive enzyme). In the presence of HDP there was significant ecoli killing however not with the addition of pancreatin.

Choi JY, Jung JH, Kwon HW, Shin S, Kim YH, Han DJ (2018). Does Enteric Conversion Affect Graft Survival After Pancreas Transplantation with Bladder Drainage? Ann Transplant. 23:89-97. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29391389/.

- 1999 to 2015, 318 pancreas transplants, 180 of which had bladder-drained transplants. Of the 180, 82 had enteric conversion at ~20 months post-txp and the remainder did not.
- Graft survival rate significantly higher for the enteric-converted group for 10 years compared to those that remained with bladder drainage.

Siskind E, et al (2018). Bladder Versus Enteric Drainage of Exocrine Secretions in Pancreas Transplantation: A Retrospective Analysis of the United Network for Organ Sharing Database. Pancreas, 47(5):625-630. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29683972.

- Retrospective analysis of UNOS data composed of 19,934 pancreas and kidney-pancreas transplant recipients transplanted between 1996 and 2012 comparing patients who received transplants with enteric drainage with Roux-en-Y, enteric drainage without Roux-en-Y, and bladder drainage.
- Unadjusted results showed improved patient and graft survival with enteric drainage without Roux-en-Y compared with enteric drainage with Roux-en-Y and bladder drainage consistent up to 15 years after transplant.

Senaratne NV, Norris JM (2015). Bladder vs enteric drainage following pancreatic transplantation: How best to support graft survival? A best evidence topic. Int J Surg. 22:149-52. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26343973.

- Best evidence topic that reviewed four retrospective cohort studies that compare enteric and bladder exocrine drainage. The authors concluded that graft survival at 1 year is comparable between the two methods of exocrine drainage.

Jiménez-Romero C, et al (2009). Comparative study of bladder versus enteric drainage in pancreas transplantation. Transplant Proc. 41(6):2466-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/19715953.

- Single center, retrospective study of 118 patients undergoing SPK or PAK who were transplanted between March 1995 to September 2008 who were managed with either enteric or bladder drainage
- Higher rates of graft thrombosis and urinary tract infections were identified in the bladder drained group compared with the enteric-drained group. There was no significant difference in the incidence of graft loss between the two groups. Three-year patient and graft survival were not different between the two groups.

Adamec M, et al (2004). A prospective comparison of bladder versus enteric drainage in vascularized pancreas transplantation. Transplant Proc. 36(4):1093-4. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15194380.

- Prospective, randomized, single center study of 40 pancreas transplant recipients comparing bladder versus enteric drainage between October 1999 and January 2002
- No difference in length of hospital stay, patient survival, graft survival, rejection, or infection rates. Increase incidence of dehydration, metabolic acidosis, and urologic complications in patients who received a bladder-drained pancreas.

Corry RJ, Chakrabarti P, Shapiro R, Jordan ML, Scantlebury VP, Vivas CA (2001). Comparison of enteric versus bladder drainage in pancreas transplantation. Transplant Proc. 33(12):1647-51. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11267454.

- Prospective, single-center trial of 243 patients transplanted (simultaneous kidney pancreas, pancreas after kidney, and pancreas alone transplants) between July 1994 and April 2000
- Overall survival was higher in the enteric drained group; however, survival was higher in the bladder drained group in the solitary pancreas patients. No difference was seen in the SKPT group. Survival rates were also lower with cold ischemia times greater than 20 hours compared to less than 15 hours. Complication rates, including relaparotomy and anastomotic bleeding requiring transfusion in were higher in the bladder drained group.

Lo A, et al (2001). Long-term outcomes in simultaneous kidney-pancreas transplant recipients with portal-enteric versus systemic-bladder drainage. Transplant Proc. 33(1-2):1684-6. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11267468.

- Retrospective, single-center analysis of 78 SKPT patients transplanted between January 1990 and January 1996 managed with either portal-enteric or systemic-bladder drainage
- There were no differences in kidney and pancreas survival rates at 5 years; however, there was significantly higher kidney graft survival in the portal-enteric group at 10 years. There was no difference in patient survival at any time point. There was a non-significant trend toward improved patient and graft survival, less metabolic complications, morbidity and better quality of life in the portal-enteric drainage group.

Stratta RJ, et al (2000). A prospective comparison of systemic-bladder versus portal-enteric drainage in vascularized pancreas transplantation. Surgery, 127(2):217-26. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/10686988.

- A prospective, single center study of 32 pancreas transplants from 1997 to 1998 randomized to receive systemic anastomosis with bladder drain or portal anastomosis with enteric drain.
- Patient survival, graft loss, hospital length of stay, and overall infectious complications were similar between groups at a mean follow-up time point of 8 months. There was a non-statistically significant increase in number of readmissions, and urinary tract infections and a statistically significant increase in metabolic acidosis, and dehydration in the patients who received a bladder drained pancreas.

2.9. Systemic versus portal venous anastomosis

Siskind E, et al (2019). A comparison of portal venous versus systemic venous drainage in pancreas transplantation. HPB (Oxford). 21(2):195-203. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30166090/

- Retrospective database review of UNOS data on adults receiving pancreas and SPK transplants from 1987-2016 were analyzed
- No significant difference in graft or patient survival at 1,3,5,10 or 15-years between groups. In a subgroup analysis of patients undergoing pancreas after kidney transplant, portal venous drainage was associated with a reduced risk of death compared to systemic venous drainage

Oliver JB, Beidas AK, Bongu A, Brown L, Shapiro ME (2015). A comparison of long-term outcomes of portal versus systemic venous drainage in pancreatic transplantation: a systematic review and meta-analysis. Clin Transplant. 29(10):882-92. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26172035.

- Systematic review and meta-analyses of 15 studies published regarding systemic versus portal vein drainage between 1989 and 2014
- No difference in fasting blood glucose levels, hemoglobin A1c, or C-peptide were seen. No difference was seen between lipid panels in either group.

Bazerbachi F, et al (2012). Portal venous versus systemic venous drainage of pancreas grafts: impact on long-term results. Am J Transplant. 12(1):226-32. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22054257.

- Retrospective, single center study of 192 SPK transplant recipients between November 1995 to November 2007 who received either portal or systemic venous drainage.
- No difference between groups in regards to patient or allograft survival, or kidney function at 1, 5, 7, and 10 years post-transplant.

Philosophe BP, et al (2001). Superiority of portal venous drainage over systemic venous drainage in pancreas transplantation. Ann. Surg. 234(5):689-696. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11685034

- Prospective, single center study of 117 simultaneous kidney and pancreas transplant recipients between August 1995 and June 2000 who received either systemic venous enteric or portal venous enteric drainage
- Overall 36-month patient survival was similar between groups. Thirty-six-month graft survival was higher and rejection rates were lower in the portal venous drainage group.

2.10. Anastomosis leak, thrombosis, or bleed post-pancreas transplantation

Innes A, et al (2021). Use of Dextran 40 After Pancreas Transplant May Reduce Early Inflammation and Significant Bleeding Compared to a Heparin-Based Protocol. Transplant Proc. 53(2):712-715. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33308839/.

- Retrospective review of 26 patients receiving a heparin-based protocol and 37 patients received D40 protocol
- Patients in the D40 group had similar thrombosis rates but were less likely to have had graft loss as a result of thrombosis or substantial postoperative bleeding. Those who received D40 had significantly lower CRP and WCC on days 2, 3, and 7.

Masset C, et al (2021). Clinical utility of C-peptide measurement after pancreas transplantation with especial focus on early graft thrombosis. Transpl Int. ePub ahead of print. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33733553/

- Retrospective evaluation of 384 pancreas transplantations and postoperative plasma C-peptide, adjusted C-peptide, and blood sugar levels
- Difference of aCP was significant during the first week after transplantation between patients with thrombosis and those with functional allograft: 63.2 vs 26.7 on day 1, $p=0.0003$; 61.4 vs 26.7 on day 3, $p<0.0001$; 64.8 vs 5.7 on day 7, $p<0.0001$, respectively. Glycemia had a median increase of 8% on the day of failure, whereas C-peptide and aCP had respectively a median decrease of 88% and 83%.

Shahrestani S, et al (2021). Successful expectant management of nonocclusive thrombosis in simultaneous pancreas-kidney transplantation. Transplant Proc. 53(1):371-378. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33419574/

- Single center retrospective analysis of 235 simultaneous pancreas-kidney transplants
- Managed with watchful waiting and imaging (9, 12%), therapeutic anticoagulation (12, 29%), laparotomy and graft thrombectomy (4, 10%). 16 required pancreatectomy (6.8%).
- Risk of thrombosis leading to graft loss was 11.2- fold higher in recipients with a BMI >25 (OR 11.2; 95% CI, 1.1-116.7; $p=0.043$).

Simonis SA, et al (2021). Applicability and reproducibility of the CPAT-grading system for pancreas allograft thrombosis. Eur J Radiol. 134:134:109462. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33341074/

- Retrospective study of 177 pancreas transplant recipients
- 318 computed tomography (CT) images were evaluated for pancreas allograft thrombosis (PAT) using the Cambridge pancreas allograft thrombosis (CPAT) grading system. Inter-rater

agreement expressed in the Fleiss' kappa, within clinically relevant thrombosis categories was 0.626 for Grade 2 and 0.781 for Grade 3 venous thrombosis.

Ferrer-Fabrega J, et al (2021). Early intestinal complications following pancreas transplantation: lessons learned from over 300 cases - a retrospective single-center study. Transplant Int. 34(1):139-152. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33084117/.

- Single center retrospective analysis of early intestinal complications and relation to vascular events
- 337 patients examined, 23 patients had early intestinal complications (including intestinal obstruction, paralytic ileus, intestinal fistula without anastomotic dehiscence, ischemic graft duodenum, dehiscence of a duodenojejunostomy, and anastomotic dehiscence in jejunum after pancreas transplantectomy). Of intestinal complications, 4 were associated with vascular thrombosis, with 2 graft losses.

Belga S, et al (2021). Donor Graft Cytomegalovirus Serostatus and the Risk of Arterial and Venous Thrombotic Events in Seronegative Recipients After Non-Thoracic Solid Organ Transplantation. Clin Infect Dis. 72(5):845-852. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32025704/.

- Retrospective cohort study of adult SOT CMV-seronegative patients who received allograft from a seropositive donor or a seronegative donor
- Assessed impact of CMV exposure at transplantation on the rate of posttransplant thrombotic events. A CMV D+/R- transplantation was independently associated with an increased risk of a thrombotic event over 5 years (adjusted hazard ratio, 3.027; 95% confidence interval, 1.669-5.488).

Van Mellaert A, et al (2020). Delayed bleeding of the transplant duodenum after simultaneous kidney-pancreas transplantation: Case Series. Transplantation. 104(1):184-189. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30946219/

- Many reported post-operative complications after pancreas transplant are early complications however there is growing attention for late complications after pancreas transplant.
- Case series of 3 SPK (2 enteric-drained and 1 bladder-drained) with anastomotic bleed over 10 years from transplant (of 122 total SPK in the same time period, 1992-2018).

Blundell J, Shahrestani S, Lendzion R, Pleass HJ, Hawthorne WJ (2020). Risk factors for early pancreatic allograft thrombosis following simultaneous pancreas-kidney transplantation: a systematic review. Clin Appl Thromb Hemost. 26:1076029620942589. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7573738/

- Systematic review of the risk factors for early pancreatic allograft thrombosis following SPK transplant. Included 63 studies (39 cohort studies, 22 conference abstracts, and 2 meta-analyses)
- 1,127 thrombi were identified in 15,936 deceased donor, whole pancreas transplants, conferring a 7.07% overall thrombosis rate. Thrombosis resulted in pancreatic allograft loss in 83.3% of reported cases. This review has established significant associations between donor and recipient characteristics, procurement and preservation methodology, transplantation technique, postoperative management, and increased risk of early thrombosis in the pancreas allograft.

Ravesh Y, et al (2019). Susceptibility-directed anticoagulation after pancreas transplantation: a single-center retrospective study. Clin Transplant. 33(7):e13619. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31152563/

- Retrospective single center review of allograft thrombosis outcomes of four anticoagulation regimens (none, SQ heparin/aspirin, with or without dextran, and heparin infusion) administered to 95 SPKs or PTAs between 1/1/2015 and 11/202018.

- Recipients with or without allograft thrombosis had similar recipient and graft survival, 95% and 86%, respectively. Outcomes of prophylaxis regimens correlated with intensity of anticoagulation (increased hemorrhagic complications with IV heparin compared to no anticoagulation; higher thrombosis in regimens lacking antiplatelet therapy)

Robbins AJ, et al (2019). Portal vein thrombosis after total pancreatectomy and islet autotransplant: prophylaxis and graft impact. Pancreas, 48(10):1329-1333. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31688597/

- Single center retrospective review of the rate of portal vein thrombosis (PVT) based on pharmacologic prophylaxis protocol and impact of PVT on islet graft function after total pancreatectomy with islet autotransplantation from 2001 to 2008.
- 12 patients (6.6%) developed PVT, which resolved by 6 months after TPIAT in 10 patients. No significant difference in PVT rate between UFH and enoxaparin prophylaxis recipients, but higher thrombotic complications in enoxaparin group (6% vs 0%). No difference in islet function for patients that developed PVT versus those who did not.

David A, et al (2019). Successful thrombectomy for graft salvage after pancreas transplant venous thrombosis. Transplantation. 2019;103(10):e321-322. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31335782/

- Single case report of a 34-year-old male with a 9 year history of type 1 diabetes mellitus with ESRD who underwent an SPK complicated by a sub-occlusive thrombus within the pancreatic transplant portal vein on POD1.
- Patient underwent catheter-directed thrombolysis and thrombectomy after which he received systemic anticoagulation with IV heparin 25,000 UI per 24 h. Patient was discharged 16 days after transplant with normal functioning pancreas.

Haidar G, et al (2019). American Society of Transplantation Infectious Diseases Community of Practice. Intra-abdominal infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 33(9):e13595. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31102546/

- Guideline covers intra-abdominal infections across all organ transplants. Within pancreas transplant recipients, the duodenal anastomotic leaks can have catastrophic consequences as polymicrobial abscesses can lead to graft loss and death.

Kopp WH, et al (2019). Retrospective study on detection, treatment, and clinical outcome of graft thrombosis following pancreas transplantation. Transpl Int. 32(4):410-417. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30525250/.

- Retrospective single center review of graft thrombosis in pancreas transplants from 2014-2015. Of the 230 patients included, early graft failure occurred in 23 patients (13/23 due to graft thrombosis, 3/23 bleeding, 1/23 anastomotic leakage, 6/23 secondary to antibody mediated rejection.
- There was evidence of partial thrombosis in 59 cases (26%), of which the majority was treated with heparin and a vitamin K antagonist with graft preservation in 57/59 patients (97%).

Messner F, et al (2018). Late recurrent bleeding episodes from duodenojejunostomy after pancreas transplantation. Clin Transplant. 32(9):e13350. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30007083/

- 379 pancreas transplants from 2000-2016 analyzed, all enteric-drained. 5 patients (1.3%) developed late hemorrhagic episodes from the anastomosis (duodenojejunostomy). Clinical manifestations = decreased Hgb, hematochezia, hemodynamic instability.
- Treatment is challenging and includes endoscopy, interventional radiology, and surgery.

Aboalsamh G, Anderson P, Al-abbassi A, Mcalister V, Luke PP, Sener A (2016). Heparin infusion in simultaneous pancreas and kidney transplantation reduces graft thrombosis and improves graft survival. Clin Transplant. 30(9):1002-9. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27293140.

- A retrospective cohort analysis of 62 SPK recipients from 2004 to 2014 of patients randomized to low-dose aspirin versus unfractionated heparin infusion immediately post-transplant in addition to low-dose aspirin started on post-op day 5
- There was a statistically significant increase in graft survival and decrease in graft thrombosis in the heparin infusion group; however, there was no difference in patient survival up to 5 years after transplant. No difference was seen in the rate of postoperative anastomotic leak or hemorrhage.

Scheffert JL, Taber DJ, Pilch NA, Chavin KD, Baliga PK, Bratton CF (2014). Clinical outcomes associated with the early postoperative use of heparin in pancreas transplantation. Transplantation, 97(6):681-5. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24285337.

- A retrospective, single-center analysis of 152 pancreas transplant recipients from 2001 to 2009.
- Fifty-two patients received a heparin infusion (no specified dosing or target partial thromboplastin time). The other 100 patients received a 300 mg aspirin suppository starting on post-operative day 1 and eventually were switched to aspirin 325 mg orally daily as tolerated. The study showed no difference in overall thrombosis rates, bleeding rates, patient survival, or graft survival between groups. There was a trend towards more partial thrombosis with heparin infusion and higher rates of exploratory laparotomy; however, there was also a trend towards higher rates of graft survival and lower rates of graft loss due to thrombosis in heparin treated patients.

Farney AC, Rogers J, Stratta RJ (2012). Pancreas graft thrombosis: causes, prevention, diagnosis, and intervention. Curr Opin Organ Transplant. 17:87–92. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22186095.

- Review of the diagnosis, prevention, and management of pancreas graft thrombosis. Management focuses on the efficacy of various agents including aspirin, unfractionated and low molecular weight heparin, and warfarin.

Schenker P, et al (2009). Incidence of pancreas graft thrombosis using low molecular-weight heparin. Clin Transplant. 23: 407-414. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/19537302.

- Single-center, retrospective review of 188 pancreas transplant recipients who received low-dose IV heparin adjusted to aPTT compared to those who received once daily low molecular weight heparin at prophylactic doses.
- There was no difference in the rate of graft thrombosis (after adjusting for confounding) or major bleeding; however, the rate of graft loss and graft loss due to thrombosis was significantly higher in the unfractionated heparin group.

Hesse UJ, Meester D, Troisi R, Cathenis K, Lameire N, Hemptinne B (2005). The use of low dose octreotide prophylaxis in pancreatic transplants with enteric drainage. Results of a prospective randomized single center trial. Clin Transplant. 19(3):299-303. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15877788.

- Prospective, randomized, open label study evaluating the use of octreotide 100 mcg every 8 hours for 7 days in 40 pancreas transplant recipients compared to no medical intervention
- There was no statistically significant difference in the rates of complication posttransplant (hemorrhage, fistula formulation at the anastomotic site, pancreatitis, thrombosis) or patient and graft survival. There was a trend towards better graft survival in patients who did not receive octreotide. There was no difference in the amount of urinary amylase or lipase secreted.

Benedetti E, et al (1998). A prospective randomized clinical trial of perioperative treatment with octreotide in pancreas transplantation. Am J Surg. 175(1):14-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/9445231.

- A prospective, randomized, open label trial at a single center of 17 bladder-drained pancreas transplants. The study compared patients who received octreotide 100 mcg subcutaneously every 8 hours for 5 days post-transplant to those who received no additional therapy.
- There was significantly less technical complications, including pancreatitis, anastomotic leaks and intra-abdominal infections, in the group that received octreotide.

2.11 Management of complications following pancreas transplantation/miscellaneous

Cerise A, Chen JM, Powelson JA, Lutz AJ, Fridel JA (2021). Pancreas transplantation would be easy if the recipients were not diabetic: A practical guide to post-operative management of diabetic complications in pancreas transplant recipients. Clin Transplant. e14270. Retrieved from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/ctr.14270.

- Review describes the impact of diabetic gastroparesis and orthostatic hypotension in post-operative course of pancreas transplant patients and analyze various treatment modalities

Owen RV, et al (2021). Too Fat for Transplant? The Impact of Recipient BMI on Pancreas Transplant Outcomes. Transplantation, 105(4):905-915. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33741849/

- Retrospective study examining all UK solid organ pancreas transplants from 1994 – 2016 (n=1452)
- Multivariate analysis showed increasing recipient BMI had significant impact on graft survival (P=0.03, HR 1.04 [1.00-1.08]). Recipients on dialysis with a BMI >30 had a statistically significant decrease in both graft (P=0.002) and patient survival (P=0.015).

Bonsdorff A, et al (2021). First-day plasma amylase detects patients at risk of complications after simultaneous pancreas-kidney transplantation. Clin Transplant. e14233. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33506535/.

- Retrospective analysis of 164 simultaneous kidney-transplant recipients and their levels of first three-day plasma amylase, drain fluid amylase, C-reactive protein, C-peptide, plasma trypysinogen, and white blood cell count
- First-day plasma amylase had the best value in predicting complications. Cut off is 6 times the upper limit of normal.

Woodside KJ, et al (2021). Approach to pancreas transplant during the COVID-19 pandemic. Clin Transplant. 35(2):e14177. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33341985/

- Letter to the editor describing the impact of COVID-19 on volume of kidney transplants
- Estimated decrease of 10% in volume of kidney transplants nationwide

Shapey IM, et al (2021). Peri-transplant glycemic control as a predictor of pancreas transplant survival. Diabetes Obes Metab. 23(1):49-57. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32893472/.

- Prospective study in 123 pancreas transplant recipients examining glucose control profiles over the first 5 days postoperatively
- Glucose AUC was a significant predictor of graft failure during 3.6 years of follow up. Hyperglycemia predicted a 3-fold higher risk of graft failure [HR (95% confidence interval): 3.0 (1.1-8.0); P = .028].

Singh P, et al (2021). Chronic graft-versus-host disease in pancreas after kidney transplant recipients - an unrecognized entity. Am J Transplant. 21(2):883-888. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32805087/

- Case series describing chronic graft vs host disease occurring in recipients of pancreas after kidney transplantation

- Two case reports, one occurring at 5.5 months and 42 months after pancreas transplant. Management strategies suggested: increasing immunosuppression, plasma transfusion.